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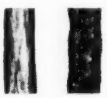

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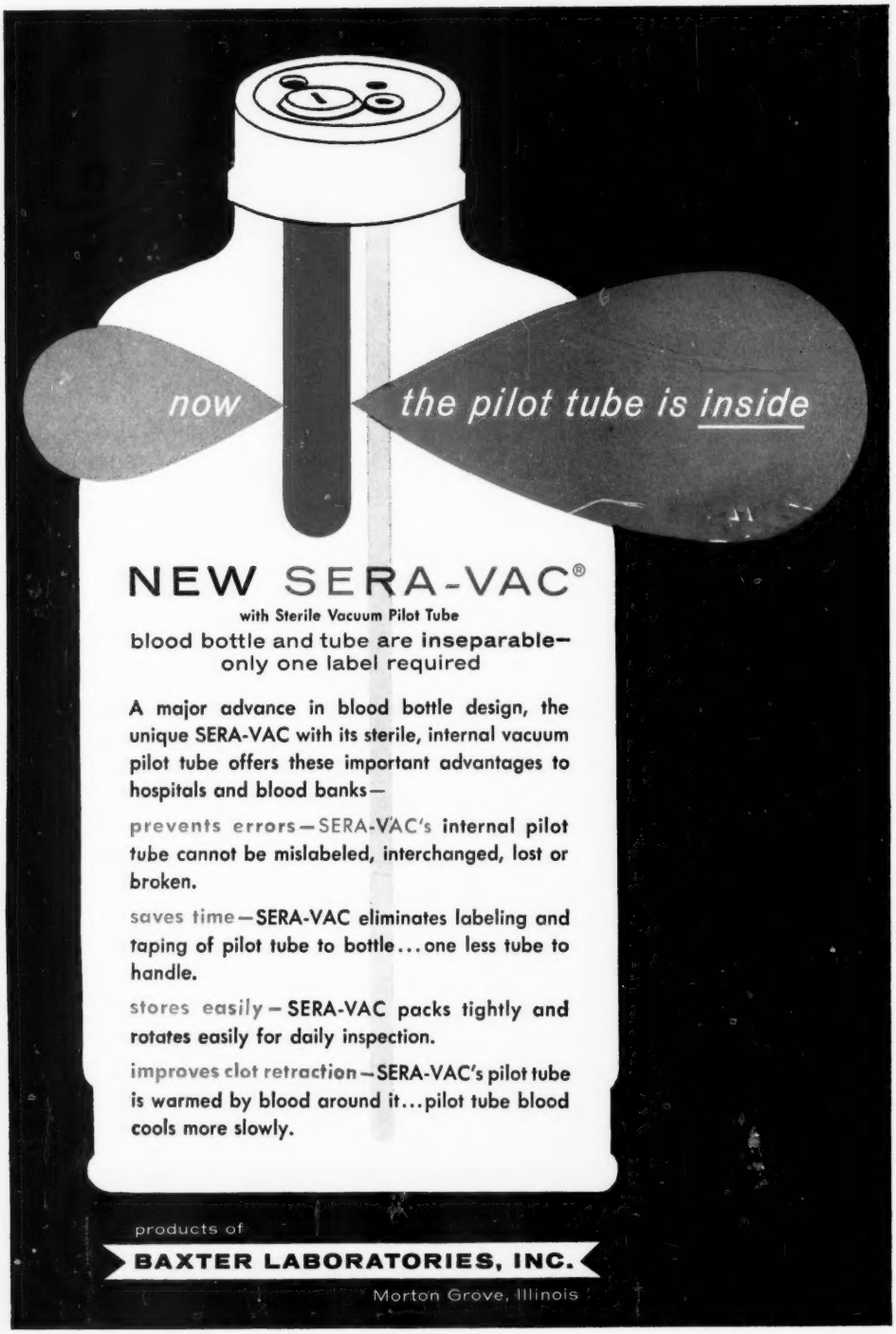
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1. Jacobson, P.: West. J. Surg. *63*:711 (Dec.) 1955.

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REPORT OF SURGICAL REPAIR IN THE FIRST GROUP OF ATOMIC RADIATION INJURIES

JAMES BARRETT BROWN, M.D., F.A.C.S., and MINOT P. FRYER, M.D., F.A.C.S.,
St. Louis, Missouri

UNDER THE TITLE of "Beta Ray Burns of Human Skin" Knowlton and co-workers in 1949 reported on 4 cases of beta ray burns of the hands for the purpose of supplementing information in the literature and of emphasizing the early clinical courses, as well as the laboratory observations in such cases.

Theirs is thought to be the first report of human damage from atomic radiation, and the present report is of the surgical care and repair of these injuries, as carried out in consultation by one of us with these authors at Los Alamos and later in St. Louis.

To recall attention to these first patients with known atomic injury (without thermal injury) we may borrow from the report of Knowlton and co-workers: "All 4 men were injured while undertaking procedures . . . at the first atomic tests at Eniwetok Atoll (United States Atomic Energy Commission's proving grounds). This work involved the handling of radioactive materials which emitted large amounts of beta and gamma radiation. A deviation in the prescribed procedure undertaken to expedite the operation resulted in the handling of these radioactive substances directly with rubber-gloved and sometimes with bare hands rather than with the remote handling devices that had been provided. Measurement of the dosage of beta rays received by the patients was not obtained at the time of exposure, but film badge and pocket ionization chambers worn by the men over the thoracic region showed readings for gamma rays varying from 1 to about 15 roentgens. In view of the fact that the hands were much closer to the active material, it must be presumed that the amount of gamma radiation received by the hands was somewhat larger, probably a factor of 10.

"The ratio of beta counts to gamma counts . . . was about 6 to 1. The physical properties of beta rays . . . are such that approximately 90 per cent of the incident rays are absorbed by the first 3 mm. of tissue and 99 per cent are absorbed in 6 mm. of tissue. Estimates of dosage indicated that these 4

From the Plastic Surgery Service, Department of Surgery, Washington University School of Medicine, St. Louis.
Work done in part under the auspices of the Atomic Energy Commission.

men received from 3,000 to 16,000 rep (roentgen equivalent physical) to the outer surface of the skin. The beta ray dosages below the surface of the skin would then be 300 to 1,600 rep at 3 mm., and 30 to 160 rep at a depth of 6 mm. . . . It was believed that there was minimal, if any, danger of important whole body effect, and the patients were treated primarily for local beta ray burns of the hands. This assumption was borne out in the course of the disease, in that at no time was there any significant evidence of other than local damage."

These 4 cases were recounted in detail by the authors (6), and their "first" report is a milestone in clinical observation and laboratory study of patients afflicted with atomic radiation injury. Anyone interested in the subject will want to study this report directly and it will not be amplified here.

A study of these first patients with atomic radiation injury (without thermal injury) is of great importance for purposes of investigation as well as for observation of their clinical course. Theirs should not be confused with other accounts, in the popular press, of patients suffering from thermal burns of atomic bomb activity. Such thermal burns are not much different from any other thermal burns and do not represent the problems or the pathology of the pure atomic radiation injury.

To recount the early course of one of the patients, Knowlton and co-workers may be quoted: "A white man aged 27 received about 15 r of gamma rays to his thoracic region and an estimated 8,000 to 16,000 rep of beta rays to his hands over a sixty minute period. During this exposure he experienced a sensation of itchiness in both hands. Four hours later . . . all the digits of the left hand were swollen and erythematous. . . . There were no blanched areas on the left hand, and the right hand appeared perfectly normal.

"During the third and fourth days, there was a definite decrease in erythema of the left hand and there were no symptoms referable to the right.

"On the twelfth day vesicles began to develop in the erythematous areas. Up to the twenty-eighth day there was spreading of the erythema, with bullae eventually forming in all such areas. By the twenty-eighth day the bullae covered the volar surfaces of all the fingers and the distal portions of the palms of both hands.

"At about this time the erythema subsided. The bullae dried up by the thirty-fifth day, and part of the dead epidermis sloughed spontaneously." Débridement was done on the thirty-ninth, fifty-third, and sixty-seventh days at Los Alamos, the areas finally demonstrating thin, glazy, tight epithelium.

All of these patients were seen in consultation, by one of us, at Los Alamos 3 months after the injuries. It was thought that the conservative care given had been correct and adequate. No amputation had been done, and there were no blood or other findings to indicate general body or blood system injury. One patient was thought to be well and possibly not to need any local treatment, with the reservation that late radiation changes might necessitate removal of the areas and grafting. One patient was more noticeably upset mentally than the others, but he made rapid improvement when hope was given for his having useful hands. For 3 of the patients it was thought that eventual resection and grafting would be needed, but no amputations were considered even though one terminal phalanx was questionable.

Comment at this consultation was, in brief: "These patients have received excellent conservative care and because of it, the best possible outcome can be expected. The records are excellent and invaluable. The question of biopsy study is still present, but such a study is thought best omitted in these hand lesions, as possibly causing too much debilitation and interference with the struggle for healing to be worth the value gained from microscopic study. (Possibly in a flat area of the body where wounds might be easily excised and the edges collapsed to-

gether, multiple biopsies could be considered and be found of importance.)

"Continued conservative treatment is encouraged, with frequent dressings—always under anesthesia when the patient desired—so that pain remembrance will be at a minimum. Letting fingers out of dressings rapidly so that the least fixation of joints may occur is recommended. Not doing forced manipulation of joints is stressed. Suggest use of white cotton gloves and cold cream locally.

"Prognosis: Possibility that chronic changes seen in the usual radiation exposures may occur and this should be guarded against, or at least be gone along with as follows: (1) avoiding further radiation exposure; (2) avoiding excess traumatic damage; (3) avoiding excess chemical damage; (4) possibly change of occupation details; (5) routine observation of exposed area over a period of years; (6) if the chronic changes become apparent, and persist to a point of telangiectasis or excessive atrophy, removal of involved areas and repair with free skin grafts; (7) joints: prognosis unknown, but probably good. Don't think they should ever be forced passively, but let moderate activity be guide to recovery and usefulness.

"The general prognosis is excellent for a normal life and normal usefulness of the hands."

Recommendations and procedures basically were conservative treatment, avoidance of amputation, subsequent removal of the involved skin, and resurfacing the areas with free skin grafts. These tenets were based on experience with radiation burns in physicians' and patients' hands, and in one, in particular, treated many years earlier and reported in 1949 (5), along with microscopic findings of various stages of radiation burns up to and including cancer formation. The most notable patient was a doctor who had sustained approximately 75,000 roentgens of x-ray exposure from an unscreened fluoroscope and who suffered acute burns almost identical with these atomic radiation burns. He had complete blistering and such severe pain as to require 6 grains of morphine a day and to plead for amputation. He was cared for by conservative treatment, at the start, and later, by resection of the areas and resurfacing with thick split skin grafts. The result was a pair of useful hands and no loss of fingers except one tip which was necrosed by the exposure. Further chronic changes around his palms developed and further grafting for these changes was necessary several years later, but the important point is that the hands were saved and the patient has been able to assume an important place in medicine in this country.

With the experience in acute x-ray burns as a background to go on, these Eniwetok atomic radiation patients have been cared for in this conservative manner.

Areas have been resected and resurfaced with free thick split grafts and good function has resulted in all the patients, no fingers have been removed, and all patients are at work in important atomic research and development. It is now 8 years since the original trouble, and the areas of damage have been grafted as they showed progress toward chronic burns. The grafting was carried out from the seventh month after the injury through the second to the fourth year. No serious changes have occurred since then and no deep losses have been noted. The patients have been urged to protect themselves, and they will be watched closely for any subsequent changes that may need removal and grafting. Any possible deep vascular damage is to be recognized early and will be guarded against by urging avoidance of chemical, radiation, mechanical, or other trauma.

As proof of the need of avoiding mechanical trauma, 1 other patient was seen with a destructive cyclotron burn of the end of a finger which healed with conservative care and because of its small size did not need grafting. The patient was advised to avoid trauma but inadvertently did injure his finger and suffered an acute secondary breakdown.

A sixth patient was seen from an Atomic Energy Commission laboratory with an

atomic radiation burn of the ankle in which natural healing had progressed about as far as it seemed it would go. This injury was treated as any radiation burn, with resection and grafting, and permanent healing resulted. Thomas L. Shipman reported that in other small beta ray burns of the fingers early grafting, performed between the tenth and fourteenth days, had given excellent results.

Observations on the incidence of radiation burns in general, source of, care of, and surgical repair of radiation burns, along with the pathology involved, have been reported by the Atomic Energy Commission, Bowers, and Brown and associates (3–5) and by other authors as well and need not be repeated here. A large volume of work of great importance has been carried out elsewhere and reported.

We believe that these experiences in surgical repair with this first group of atomic radiation injuries (without thermal injury) in this country are valuable guides for the treatment of future patients who may suffer such injury and be fortunate enough not to have full body fatal exposure.

SUMMARY

Report is made of the surgical repair of the first known group of atomic radiation injuries (without thermal injury) with the result that no amputations have been necessary and that all patients are back at full time occupations. These are injuries caused by pure atomic radiation and are not thermal injuries of atomic origin, as have been described elsewhere. If such patients do survive, it seems proved herein that their local injuries caused by atomic radiation may be repaired surgically and that successful rehabilitation is possible.

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THE SURGICAL TREATMENT OF ESOPHAGEAL STRICTURE

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Minneapolis, Minnesota

CLINICAL OBSERVATION and experimental investigations have emphasized the frequency with which the acid-peptic diathesis is responsible for esophagitis, esophageal ulcer, and spontaneous esophageal perforation. That "idiopathic" lower esophageal stricture is also acid-peptic linked was suggested by the striking benefit achieved by subtotal gastrectomy in a group of patients with this disease treated in this clinic and reported in 1949(11). It is the purpose of the present communication to summarize the long term follow-up of the 6 patients originally reported upon and to describe further clinical experience in an additional 12 patients similarly treated. A summary of predisposing factors, operative procedure, follow-up period, and clinical and roentgenographic results appears in Table I. Illustrative case histories with preoperative and postoperative roentgenograms of the esophagus follow. Cases 1 and 6 were detailed in the original report(11).

CASE HISTORIES

CASE 1. L. W., a 53 year old male, was seen many times at the University Hospital between 1935 and 1939 with complaints referable to an obstructing and bleeding duodenal ulcer. Dysphagia developed in February 1936, and an esophagogram revealed a lower esophageal stricture which was confirmed by esophagoscopy. The patient was treated with a Sippy diet and esophageal dilatations once or twice a month until August 1939 at which time a subtotal gastrectomy was performed for severe gastrointestinal hemorrhage. It was not anticipated that esophageal dilatations could be discontinued following this surgical procedure. However, only 2 dilatations were required in the convalescent period whereas in the 3½ year period preceding surgery, over 100 dilatations had not been successful in controlling the dysphagia. In 1940, a No. 45 dilator was passed with ease as a diagnostic test of esophageal lumen size. The patient has had no recurrence of dysphagia or gastrointestinal hemorrhage during the 16 year follow-up period and has not required esophageal dilatation. The patient eats all foods without any difficulty whatsoever. Esophagograms before and after subtotal gastrectomy are illustrated in Fig. 1a and b.

CASE 6. H. B., a 47 year old male, was first seen at the University Hospitals in 1947 with complaints referable to a duodenal ulcer since 1911. In 1940 a perforated duodenal ulcer was closed surgically. Six weeks following this procedure dysphagia developed and progressed rapidly so that in 2 months he lost 40 pounds. A gastrostomy had been performed elsewhere at which time the patient was unable to swallow his saliva.

In July 1947, an esophagogram was attempted but was unsatisfactory because of the severity of the stenosis. Dilatations ultimately were accomplished by using a No. 5 French ureteral catheter initially which was brought out through the gastrostomy. Esophagogram following dilatation to No. 29 French sound showed a severe stricture extending down from the midesophagus to the stomach (Fig. 2a). Dilatations provoked burning substernal pain. However, he was able to swallow liquids.

In January 1948, another perforation of duodenal ulcer occurred which was treated nonoperatively, but was followed by pyloric and more severe, esophageal obstruction. Subtotal gastric resection was performed on March 19, 1948. Prior to discharge from the hospital, a No. 29 French dilator was passed through the stricture. In the subsequent 6 weeks the dysphagia improved greatly. Whereas, an esophagogram made on March 30, 1948 (Fig. 2b) showed only a trickle of barium entering the stomach because of esophageal stricture, considerable improvement was apparent by May 10, 1948 (2 months postoperatively) and barium swallow 3 years later on September 4, 1951 showed no evidence of obstruction (Fig. 2c). The patient has not experienced any dysphagia since the summer of 1948 and has not received dilatations since that time. He ingests a normal diet without any precaution as to food particle size.

From the Department of Surgery, University of Minnesota Medical School, Minneapolis. Supported by the U. S. Public Health Service, Grant No. A 382 C, the Graduate School Fund, and the Austen S. and Anne R. Cargill Fund.

TABLE I.—RESULTS OF TREATMENT OF ACID-PEPTIC STRICTURE OF THE ESOPHAGUS

Patient No. Age at follow-up, yrs.	*Predisposition*	*Operation**	*Follow-up period, yrs.*	*Swallowing†*	*Last esophagogram*	*Preoperative free gastric acid‡*	*Postoperative free gastric acid*
L.W. 1 68	Duodenal ulcer Pyloric obstruction	III	16	A	Normal	38°-F	—
C.V.D. 2 90	Duodenal ulcer Pyloric obstruction	IVA	5	A	Slight narrowing. No obstruction	—	—
E.K. 3 72	Unknown	III	9	A	Minimal deformity. No obstruction	34°-H	—
C.G. 4 25	Unknown	III	8	A	No stricture. No obstruction	60°-H	0°-H
V.G. 5 62	Gastric ulcer	III	7	A	Normal	100°-H	—
H.B. 6 54	Duodenal ulcer Pyloric obstruction	III	7	A	Tapered lower oesophagus. No obstruction	74°-H	—
S.N. 7 79	Duodenal ulcer Hiatal hernia	III	3.5	A	Slight narrowing. No obstruction	40°-H	—
T.S. 8 64	Hiatal hernia	Segmental	4	B	Minimal deformity. No obstruction	22°-A	0°-H
H.S. 9 48	Hiatal hernia	Tubular + H.M.	3	A	Slight distortion. No obstruction	52°-H	0°-H
F.W. 10 71	Unknown	Tubular + H.M.	3	A	Normal	179°-H	52°-H
T.N. 11 75	Duodenal ulcer	III	3	A	Minimal irregularity. No obstruction	52°-H	—
O.J. 12 60	Duodenal ulcer	Tubular + H.M.	2	A	Residual stricture. Improved	71°-H	7°-H
A.W. 13 65	Hiatal hernia	Tubular + H.M.	2	B	Esophageal stricture. Some improvement	73°-H	0°-H
A.L. 14 47	Unknown	Tubular + H.M.	1	B	Esophageal stricture. Slight improvement	—	—
H.M. 15 67	Hiatal hernia Pylorospasm	Hernia repair and H.M.	1	B	Normal	—	—
H.S. 16 73	Hiatal hernia	Hernia repair and H.M.	½	A	Minimal deformity. No obstruction	40°	—
W.C. 17 56	Hiatal hernia Pylorospasm	Hernia repair and H.M.	½	A	Minimal deformity. No obstruction	93°-H	—
M.K. 18 53	Hiatal hernia	Tubular and H.M.	4/12	B	Minimal deformity. No obstruction	—	—
F.O. 19 47	Concentrated hydrochloric Acid	Segmental + H.M.	1 3/12	C	Slight increase in esophageal lumen	—	—

*Nomenclature: III, ¾ distal gastrectomy with Hofmeister retrocolic gastrojejunostomy.
IVA, Finsterer exclusion operation with removal of the antral mucosa.
Segmental, Segmental gastric resection.
Tubular, Tubular gastric resection.
H.M., Heineke-Mikulicz pyloroplasty.

†Postoperative swallowing:
A, Ability to ingest all foods without dysphagia at any time.
B, Ability to ingest all foods with dysphagia on rare occasions (no oftener than once a month).
C, Dysphagia—improved.
D, Dysphagia—no improvement.

‡F, fasting.
H, with histamine stimulation.
A, with alcohol stimulation.

CASE 8. T. S., a 61 year old female, was first seen at the University Hospitals on April 18, 1951 with the complaint of dysphagia for 1 year. This had been preceded by postprandial heartburn especially when lying down. The dysphagia became progressively more severe so that liquids only could be ingested. A 16 pound weight loss occurred in the 4 months prior to admission, even though she was closely supervised on a bland diet, antacids, and antispasmodics, a regimen which in no way altered the dysphagia.

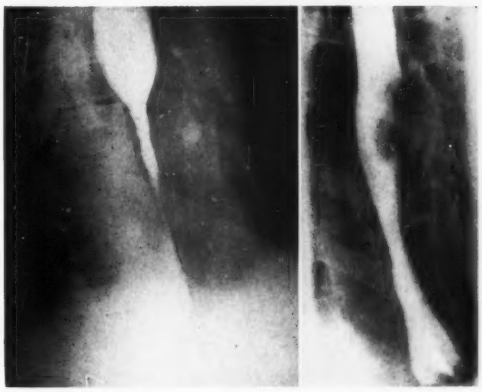
Gastrointestinal x-ray examination on April 20, 1951 revealed a large, easily reducible hiatal hernia with narrowing and irregularity of the distal esophagus (Fig. 3a). Three months later a lower esophageal ulcer had developed. Esophagoscopy confirmed the diagnosis of esophagitis with stricture. The patient had 22 degrees of free gastric acid on alcohol stimulation. On August 14, 1951, a segmental gastric resection, Heineke-Mikulicz pyloroplasty, and hiatal hernia repair were performed with an extensive excision of the acid-producing area of the stomach. The patient had an immediate and excellent response to surgery and has not experienced dysphagia or heartburn since, except on the rarest occasions when excited.

Roentgenograms of the esophagus made on July 29, 1953, 2 years after operation, revealed prompt passage through the esophagus without delay, and without evidence of constriction. (Fig. 3b).

Gastroesophageal regurgitation has persisted in spite of hiatal hernia repair. A postoperative gastric analysis made on February 4, 1954 revealed no free acid with triple histamine stimulation. The patient continues without complaint and ingests a full diet at the present time (October 1955).

CASE 10. F. W., a 69 year old man, was admitted to the University Hospitals on May 7, 1952 with the complaint of progressive dysphagia of 6 months' duration. He was unable to eat any solids at the time of admission and had been troubled with heartburn for many years. An esophagogram taken on May 8, 1952 showed a lower esophageal stricture with hiatal hernia (Fig 4a). An annular stenosing lesion located at 34 centimeters from the upper alveolar ridge was visualized on esophagoscopy. A No. 14 French lumen finder was passed through the stenosed area with considerable difficulty. Biopsy of the strictured area revealed inflammation and a chronic ulcer of the esophagus. Gastric analysis showed the very high free acid on histamine stimulation of 179 degrees.

On May 14, 1952 a tubular gastrectomy with Heineke-Mikulicz pyloroplasty was performed. There was no evidence of hiatal hernia. For 2 months following the operation the patient occasionally noted that some solid foods "stuck." He was no longer troubled with heartburn. An esophagogram made on July 10, 1952, 3 months after operation, showed a narrowed area in the lower third of the esophagus with improvement from the previous examination. On February 24, 1954 an esophagogram showed no evidence of stricture (Fig. 4b). The patient is able to eat all foods without difficulty. Gastric analysis since surgery revealed 52 degrees of free acid with histamine stimulation. A No. 41 French dilator passes through the esophagus with ease. The patient does not require dilatations.

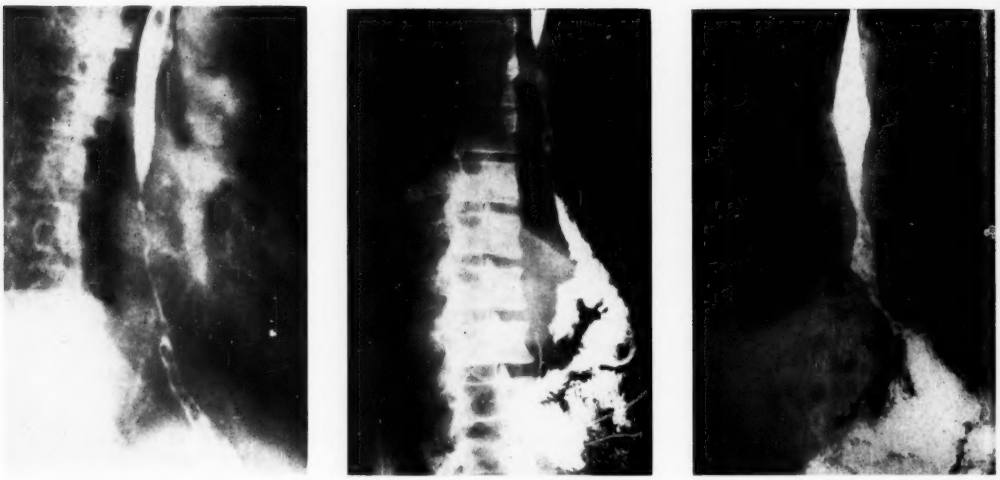


a b

FIG. 1. Case 1. a, Esophagogram made on April 1, 1936 prior to gastric resection during period of dilatations; b, normal esophagogram, April 1954. There is no esophageal stricture or delay in passage of thin or thick barium. The patient is asymptomatic 16 years after subtotal gastric resection.

DISCUSSION

A total of 19 patients with lower esophageal stricture have been treated by a procedure designed to decrease acid-peptic irritation of the lower esophagus. Sixteen patients underwent subtotal gastrectomy, and 3 were treated with hiatal hernia repair by a previously described method (9) with pyloroplasty. The factor predisposing to lower esophageal stricture was either gastric or duodenal ulcer in 6 patients, hiatal hernia in 7 patients, both duodenal ulcer and hiatal hernia in 1 patient, and unknown in 4 patients. One patient with a severe constriction of the esophagus which extended from the aortic arch to the stomach, the result of the ingestion of concentrated hydrochloric acid with suicidal intent was also treated by subtotal gastric resection. Esophagograms demonstrated an increase in the size of the esophageal lumen following the operation. Unfortunately, after returning home this patient became depressed, re-



a b c

FIG. 2.

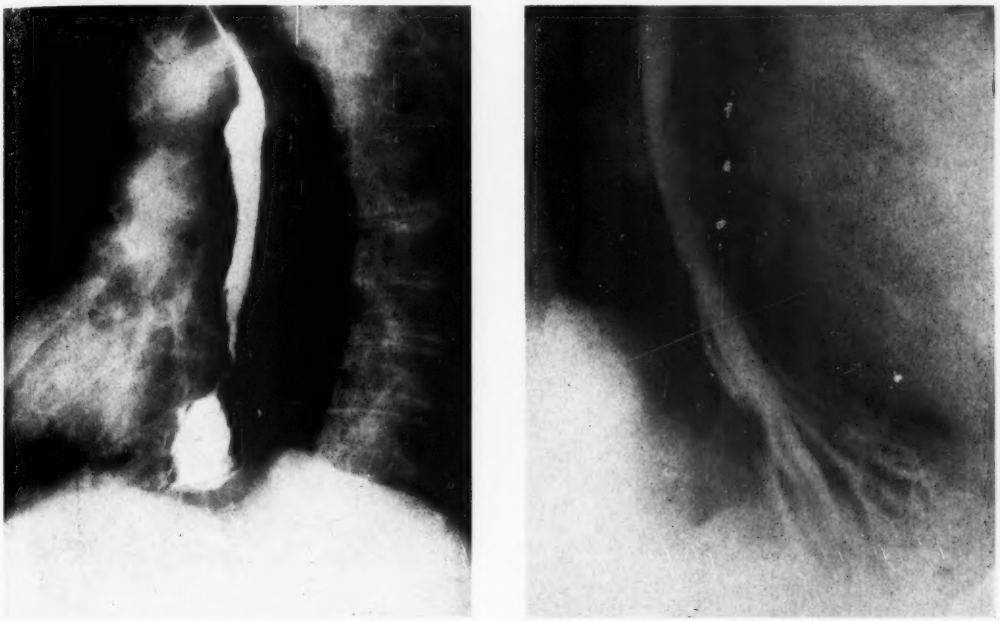
a b

FIG. 3.

FIG. 2. Case 6. a, Esophagogram made in July 1947 (preoperative) following dilatation to No. 29 French sound reveals a severe stricture extending from the mid-esophagus to the stomach; b, esophagogram made March 30, 1948 (2 weeks after operation) reveals slight improvement. The patient was greatly improved clinically at this time. c, Esophagogram made September 4, 1951 reveals no evidence of obstruction. The patient has had no dysphagia since 2 months following subtotal gastrectomy.

FIG. 3. Case 8. a, Esophagogram made July 24, 1951 shows marked stricture. The patient experienced severe dysphagia and was malnourished at that time; b, esophagogram made July 29, 1953 shows minimal deformity, and no evidence of obstruction 2 years following the operation.

fused to eat, and expired 14 months following operation. With this single exception, esophageal lumen size has been greatly improved or has returned to normal in all patients. Those postoperative esophagograms which have revealed some deformity are greatly improved, and no obstruction to the flow of thick barium has been observed in contrast to preoperative findings. Symptomatic benefits have likewise been remarkable. Thirteen of the patients have completely normal swallowing with all foods at all times despite severe dysphagia prior to operation. One patient (H. B., Case 6) required a gastrostomy for feeding prior to gastrectomy and was unable to swallow his own saliva. It is of interest that whereas the presence of a congenitally short esophagus was diagnosed by roentgen study in several of the patients, in none of these patients was the condition observed at operation. Similarly, hiatal hernia is diagnosed occasionally by the roentgenologists in the presence of stenosing esophagitis, without



a b

FIG. 4. Case 10. a, Lower esophageal stricture with roentgen evidence of hiatal hernia. The latter was not found at operation on May 14, 1952; b, normal esophagogram made February 24, 1954. The patient ingests a normal diet without dysphagia at any time.

any evidence of such a hernia being found at operation.

A high gastric acidity has been observed frequently. Uniformly, this situation has been rectified by gastrectomy. Three types of subtotal gastric resection, tubular gastrectomy (10), segmental gastrectomy (10), and the Billroth II subtotal gastrectomy have been used successfully in the treatment of lower esophageal stricture.[1] Each of these procedures includes an extensive excision of acid secreting mucosa and insurance of adequate gastric pouch emptying by a wide anastomosis or concomitant performance of a Heineke-Mikulicz pyloroplasty.

[1]When the presentation on segmental gastric resection (*J. Am. M. Ass.*, 149: 18, 1952) was made before the Surgical Section of the American Medical Association in Atlantic City (June 14, 1951), failure of the operation was predicted. The truth of the matter is that this is the only operative procedure for peptic ulcer which has not been followed by recurrent ulcer in this clinic. More than 120 such operations have now been performed (April 18, 1956); 90 of these were done more than 4 years ago. It appears that a segmental gastric resection, 70 per cent in extent of which the residual pouch is half antrum and half fundus is an extremely satisfactory operation for duodenal ulcer.

The persistence of beneficial effects is evidenced by the long follow-up period in many of the patients reported (Table I). Esophageal dilatation is usually performed once or twice in the early convalescent period when it is noted that larger dilators pass the strictured area with greater ease. The necessity of insuring a functional lumen by dilatation directly following operation is emphasized, since other observers who failed to find subtotal gastrectomy successful in the treatment of lower esophageal stricture did not venture employment of esophageal dilatation during the early recovery phase. Adequate gastric emptying must also be provided. Without adequate provision for gastric emptying, the aggravation of esophagitis, noted clinically and experimentally following vagotomy alone, results.

CLINICAL OBSERVATIONS

As early as 1852 protracted vomiting was described by Trotter as a cause of dysphagia.

a b

FIG. 5. The case of Professor Auguste of Lille, France. a, Esophagogram made in May 1942 showing extensive esophageal stricture due to the accidental ingestion of lye less than 1 month previously. b, Remarkable improvement shown in esophagogram made in March 1952 accompanied by an excellent clinical result following subtotal gastrectomy. (Courtesy of M. C. Auguste in *Archives des Maladies de l'appareil digestif* (1) and the publisher, Masson et Cie, Paris.)

The importance of acid-peptic regurgitation and vomiting in the pathogenesis of hematemesis, esophagitis, and esophageal stricture has been emphasized in earlier reviews of the subject. Palmer (4) reports complete esophageal atresia resulting from persistent, prolonged vomiting.

Another clinical observation of importance suggesting that lower esophageal stricture is often of acid-peptic origin is the frequent association of esophagitis with hiatal hernia. Parahiatal esophageal hernias, which do not interfere with the location or function of the cardia, apparently are not associated with esophagitis or esophageal stricture.

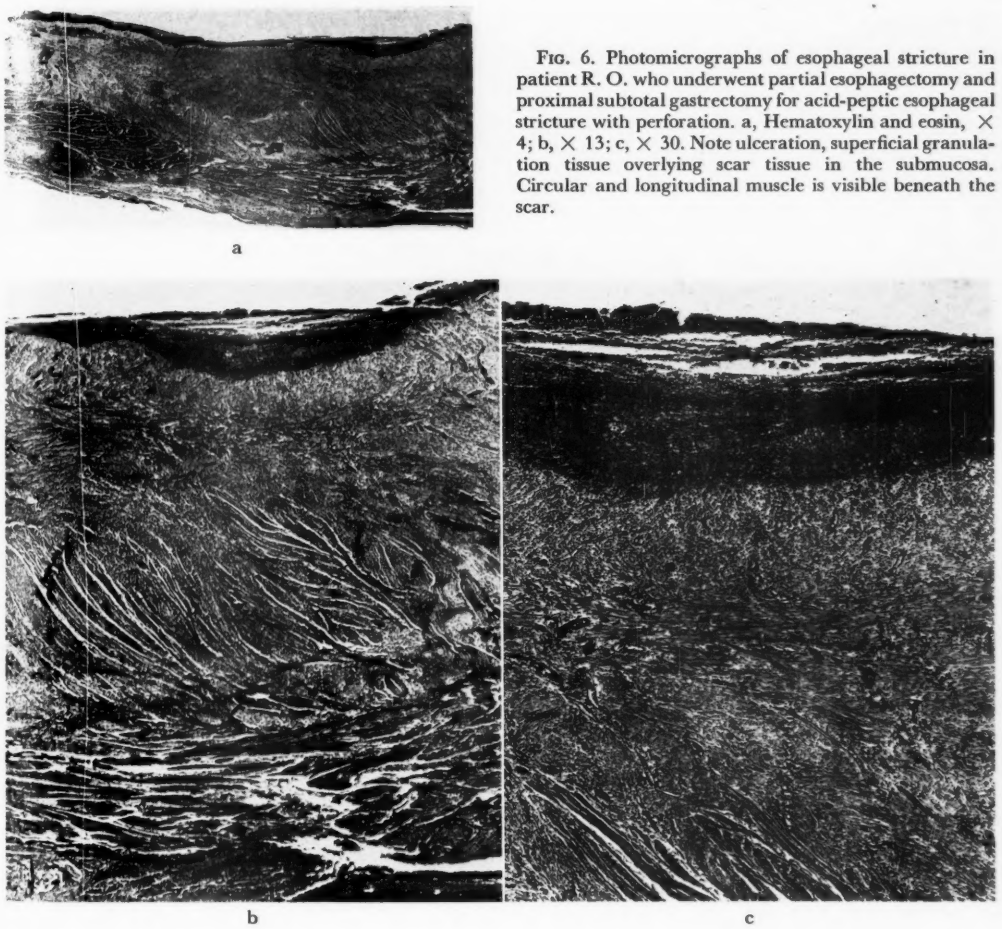
Experienced observers report that peptic ulcer of the stomach and duodenum predisposes to esophagitis, esophageal ulcer, and stricture. The combination of pyloric obstruction and high gastric acid production is especially likely to cause difficulty.

The occurrence of severe esophagitis, following the Wendel and Heyrovsky-Gröndahl operations for cardiospasm, is well known. These procedures permit the retrograde passage of gastric juice into the esophagus.

EXPERIMENTAL OBSERVATIONS

Experimental evidence further illustrates the susceptibility of esophageal mucosa to acid-peptic digestion. Selye was able to produce hemorrhagic esophagitis in rats by pyloric ligation. The production of an insufficient cardia in dogs, either by esophagogastric anastomosis or pyloric ligation plus histamine in beeswax stimulation produces extensive esophageal destruction. The stomachs of these animals remain normal despite adjacent esophageal ulceration and perforation. Prior excision of the acid-producing area of the stomach under these very same conditions protects completely against the occurrence of esophagitis or esophageal perforation. This latter circumstance speaks favorably for the acid-peptic erosion factor in the genesis of so-called "spontaneous" perforation of the esophagus. Ripley and his co-workers have produced esophageal stricture in the dog which was associated with an incompetent cardiac sphincter.

Palmer (5) has been inclined to discount the acid-peptic theory of esophagitis on the basis of esophagoscopic biopsies which show subepithelial reaction without surface erosion or ulcer. However, the accumulation of clinical and experimental evidence serves to lend renewed emphasis to the great susceptibility of the esophageal mucosa to injury by acid-peptic juice.



a

b

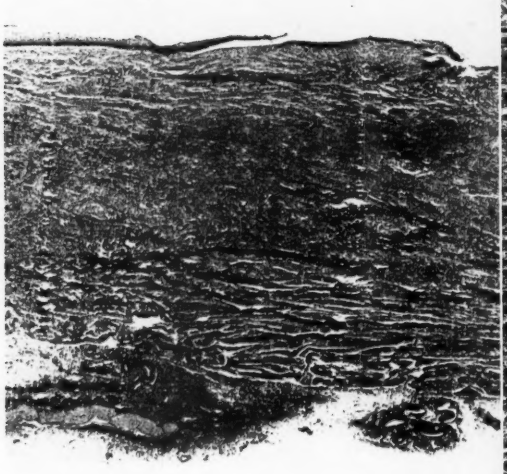
c

FIG. 6. Photomicrographs of esophageal stricture in patient R. O. who underwent partial esophagectomy and proximal subtotal gastrectomy for acid-peptic esophageal stricture with perforation. a, Hematoxylin and eosin, × 4; b, × 13; c, × 30. Note ulceration, superficial granulation tissue overlying scar tissue in the submucosa. Circular and longitudinal muscle is visible beneath the scar.

GASTRIC RESECTION IN THE MANAGEMENT OF STRICTURES OF THE ESOPHAGUS OWING TO INGESTION OF CORROSIVE AGENTS

Patient 19 (Table I) had a long esophageal stricture due to the ingestion of concentrated hydrochloric acid with suicidal intent. While the clinical response of this patient to subtotal gastrectomy was disappointing, esophagograms did reveal an increase in luminal diameter and a No. 41 French dilator could be passed whereas dilatations had been impossible immediately prior to gastric resection. Professor Auguste of Lille, France has reported a similar patient with, however, a remarkably successful ultimate result. This patient, a 45 year old man, who had a gastric ulcer demonstrated in 1939, accidentally ingested some concentrated sodium hydroxide in May 1942. A tight stricture developed which was confirmed by esophagoscopy (Fig. 5a). Dilatations helped temporarily but epigastric burning became very severe and in December 1942 a two-thirds subtotal gastrectomy was performed. By August 1944, dysphagia had disappeared and dilatations were discontinued. An esophagogram in 1952 compared to the preoperative status shows remarkable improvement (Fig. 5b). The performance of gastric resection, Professor Auguste states,

a



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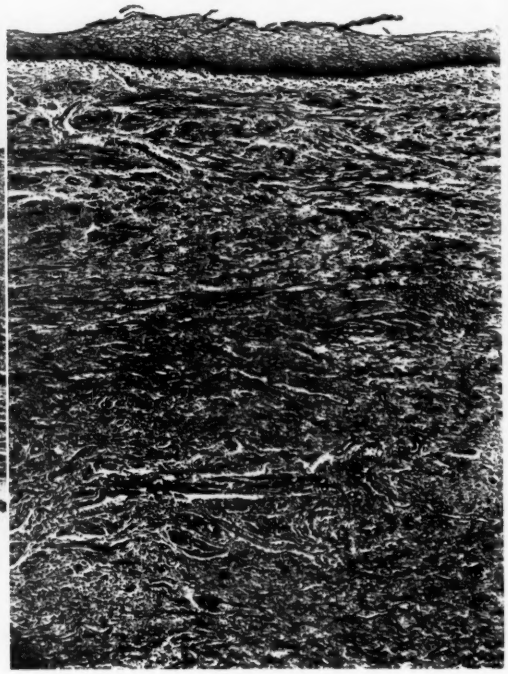

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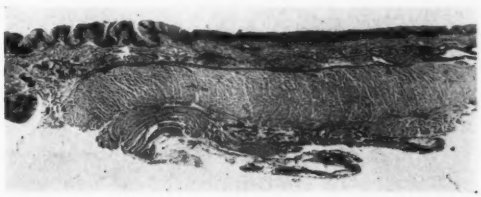
FIG. 7. Photomicrographs of esophageal stricture due to the ingestion of lye (patient L. K.). a, Hematoxylin and eosin, × 4; b, × 13; c, × 30. Note hyaline scarring of the entire esophageal wall with loss of both longitudinal and circular musculature.

brought about a better clinical result than was seen in 200 patients treated by dilatation alone between 1942 and 1952 for stricture due to ingestion of corrosive agents.

Two patients with lye and concentrated acid strictures, L. K. and W. G., have been treated in this clinic by resection of the esophageal stricture with esophagogastric anastomosis in the right thorax (L. K.) and in the right neck (W. G.). In addition, a Heineke-Mikulicz pyloroplasty was performed to facilitate gastric emptying. The relief of dysphagia was immediate in both patients, and has remained so for 2.5 and 4 years since operation. While the esophagogastric anastomosis was very high in 1 of these patients (W. G.) the complication of loss of the sphincteric mechanism between the pharynx and stomach as reported by Gross was not encountered. The insertion of a 4 hole nasal tube on suction into the pharynx may be useful to demonstrate the highest level at which resection can be performed without disruption of the pharyngeal sphincter with ingestion of air with each breath. This is usually remarkably high, approximately 20 centimeters from the external nasal aperture in the adult.

Paine in 1951, on surveying the American literature, could find only 16 cases of re-



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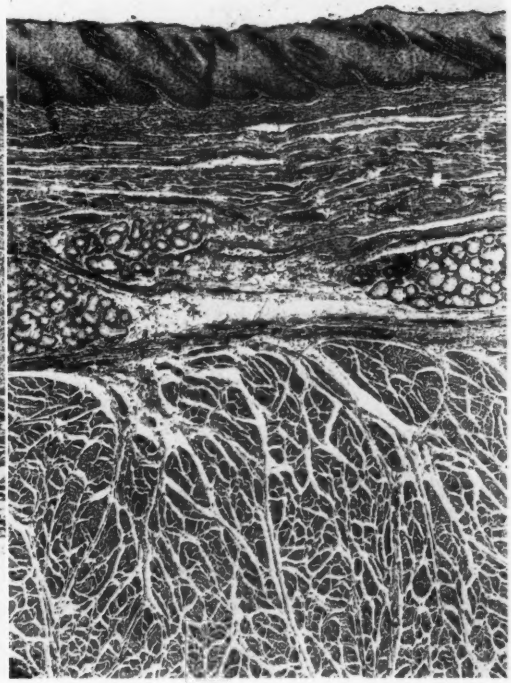

c

FIG. 8. Photomicrographs of normal esophagus. a, Hematoxylin and eosin, × 4; b, × 13; c, × 30. Note normal thickness of submucosa and muscular layers for comparison with Figures 6 and 7. The submucosal glands present normally in the lower esophagus are not seen following esophagitis.

section of lye strictures of the esophagus with restoration of gastrointestinal continuity. He reported 2 additional cases with very satisfactory results.

The prompt relief of dysphagia, the lesser economic burden, and the uniformly better results definitely recommend esophageal resection over dilatation in the management of corrosive strictures of the esophagus.

THE RATIONALE OF ALLEVIATION OF ESOPHAGEAL STRICTURE BY GASTRIC RESECTION

That reduction of the stomach's capacity to secrete acid-peptic juice accompanied by provision for ready gastric emptying will minimize, if not eliminate completely, the opportunity for regurgitation of gastric juice into the esophagus is understandable. That strictures such as those shown in Figure 6 will disappear following gastric resection with the aid of a few esophageal dilatations during the first few weeks of convalescence is not so readily understood. It would appear that the answer should lie in the depth of the lesion in the esophageal wall.

A study comparing the histologic changes in the esophageal wall observed in acid-peptic stricture with those occurring following the ingestion of erosive agents could

serve to shed helpful light on the behavior of acid-peptic esophageal strictures following gastric resection. One such stricture is available for comparison in Figure 7 and a normal esophagus is illustrated in Figure 8. It would appear that the fibrotic process permeates all the walls of the corrosive stricture as contrasted with the acid-peptic stricture in which the injury appears to be delimited to the mucosa and submucosa. Obviously, this phase of the inquiry will require a careful and detailed histologic study of many acid-peptic esophageal strictures. And fortunately, such materials are available, for resection of the stricture has been the operation of choice in many clinics.

SUMMARY AND CONCLUSIONS

1. Eighteen patients with esophageal stricture have been treated by a surgical procedure designed to decrease acid-peptic irritation of the lower esophagus. Fifteen patients underwent subtotal gastrectomy and in 3 hiatal hernia repair accompanied by a Heineke-Mikulicz pyloroplasty was performed. In all 18 patients, complete disappearance (13 patients, graded A) or substantial improvement (5 patients, graded B) in dysphagia occurred. The period of observation following operation ranges from 4 months to 16 years. Gastric resection was carried out in 1 patient with an extensive corrosive stricture of the esophagus, with but slight improvement.

2. An accompanying gastric or duodenal ulcer was observed in 6 patients having acid-peptic strictures of the esophagus; hiatal hernia was present in 7 patients; both duodenal ulcer and hiatal hernia in 1 patient, and in 4 patients no concomitant anatomic abnormality was detected.

3. Re-establishment of a fairly normal esophagogram following gastric resection was observed in even the most deformed and strictured esophagi in the follow-up roentgenograms which were taken over a period of months.

4. The esophageal lumen size, as estimated by the size of dilator which traverses the strictured area, increased markedly in the immediate and early postoperative period.

5. Preliminary microscopic studies suggest that the depth of the esophageal lesion in acid-peptic esophageal stricture involves primarily the superficial layers of the esophageal wall (mucosa and submucosa) as contrasted with the stricture which results from the ingestion of corrosive caustic agents in which the entire esophageal wall becomes involved in the fibrotic process.

6. Gastric acid production frequently is elevated in patients with esophageal stricture.

7. Esophageal resection with intrathoracic or cervical esophagogastrostomy is recommended for lye or concentrated acid stricture. Two patients who were incapacitated and without lasting benefit from dilatations have been restored to full health following resection of the esophageal stricture.

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PROLONGED FUNCTIONAL SURVIVAL OF RENAL AUTOTRANSPLANTS IN THE DOG

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OUR EXPERIENCE with renal autotransplants in dogs differs from that of others. From Carrel's day to the present, investigators have noted impairment of water-load excretion, concentration ability, and other functions in autotransplants. Recently, Dempster noted that the use of the pelvis as the recipient site improved the function of the graft. Our observations indicate that autografts function well and may survive indefinitely.

These observations assume added significance as kidney homotransplantation in man is being more fully explored and understood. The aims of present investigation in homotransplantation might be considered as attempts to overcome the immunologic and genetic differences between individuals of the same species and to make homografts behave as autografts. Whenever these barriers are surmounted, as in the recent instance of the transplantation of a kidney from one to the other of twins whose genetic and immunologic identity had been established, the question of the prolonged function of the graft becomes of major importance (5, 7). Most experimental data indicated that renal autografts did not function normally. The anatomic site selected for the graft or possibly the denervation of the transplant was considered to have an effect on this impairment of function.

The observations reported in this article indicate that a renal transplant, free of genetic and immunologic incompatibilities, totally denervated, revascularized in an anatomic site having the same temperature as the renal fossa, and with a direct implantation of the ureter into the bladder can survive without detectable impairment of function indefinitely.

The earlier human renal homotransplants were connected to the femoral vessels in the upper thigh in order to minimize the operative and postoperative morbidity, and to allow easier access to the kidney for biopsy or removal. A skin ureterostomy connected to a collecting bag attached to the leg allowed the separate measurement of function. The probability of infection and the inconvenience with urine collection precluded the use of this site when the likelihood for permanent success seemed certain. Therefore, in the case of the identical twins, an intra-abdominal site which permitted a ureterovesical anastomosis was selected based on the observations to be described in this article.

Early in our preparation for experiments with homologous renal transplantation, autologous transplants were prepared to perfect the technique and to serve as control material (6). The usual recipient sites were tried; i.e. the neck, renal fossa, and the pelvic area. A neck kidney with a cutaneous ureterostomy invariably developed hydronephrosis with or without infection, probably related to the constant motion of the neck. A kidney transplanted to the renal fossa with a cutaneous ureterostomy developed infection after several months. The

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TABLE I.—BLOOD UREA NITROGEN AND URINARY SPECIFIC GRAVITIES AFTER AUTOTRANSPLANTED KIDNEYS IN DOGS

Dog	*Date of transplant*	*Date of observation*	*B.U.N., mgm. per cent*	*Specific gravity*
141-52	7-30-52	8- 3-52	34.6	
		8-12-52	22.9	
		10-18-54		1.060
		10-28-54		1.058*
		10-29-54		1.056
		10-30-54	20.0	1.021
130-52	7-16-52	7-22-52	39.0	
		8-13-52	11.5	
		10-28-54		1.021*
		10-29-54	11.0	1.013
		11- 2-54		1.036
2-52	1- 2-52	10-28-54		1.033*
		10-29-54	11.0	1.013
		10-30-54		1.044
		10-31-54		1.042

*After 12 hours' water deprivation.

pelvis was selected as the recipient site of choice, the anastomoses being made between the iliac vessels and the renal vessels, with the ureter implanted directly into the bladder.

Without planning, 3 animals, from many successfully autografted, had not been sacrificed after 1 year. In these dogs the functional capacity of the autograft as an only kidney was observed as late as 2½ years after transplantation.

OPERATIVE TECHNIQUE

Mongrel dogs weighing 10 to 14 kilograms were anesthetized with phenobarbital sodium (30 mgm. per kgm. of body weight) intravenously. Through a midline abdominal incision a left nephrectomy was performed and the kidney discarded. Next the right kidney pedicle was isolated and the renal artery, renal vein, and the ureter were ligated and divided. This kidney after removal was wrapped in a moist sponge at room temperature until ready for use.

The right common iliac artery and vein were ligated and divided approximately 2 centimeters distal to the aortic bifurcation, bulldog clamps being placed proximally, and end-to-end anastomoses were performed with the renal artery and renal vein respectively by using the surgical technique originally described by Carrel. The distal tip of the ureter was incised longitudinally for a distance of ½ centimeter and implanted into the urinary bladder through a stab wound. The anastomotic sites were selected carefully to prevent buckling or twisting of the vessels as the kidney was placed in the hollow of the lateral peritoneal surface. The ureteral segment, about 7 centimeters in length, passed easily to the bladder without kinking. A suture through the pericapsular tissue fixed the kidney to the peritoneal wall.

The usual period between removal of the kidney from the renal fossa and establishment of the blood supply with the pelvic vessels was 30 minutes. Both anastomoses were completed before blood was allowed to flow through the kidney. Discrepancies between the size of the renal artery and iliac artery usually required cutting the renal artery obliquely to obtain greater circumference.

Thus the only kidney in the animal was an autotransplant with the ureter reconnected to the bladder. This technique proved consistently satisfactory without early or late complications.

POSTOPERATIVE OBSERVATION AND FUNCTION TESTS

After recovery from anesthesia the animals behaved normally, being frisky, alert, and eating well. The typical early response of a dog to autotransplantation of one kidney after removal of the opposite one is depicted in Figure 1. Note the return to normal of the specific gravity, urine volume, and blood urea nitrogen within 30 days. One animal (2-52) 2 years postoperatively gave birth to a litter of 9 normal puppies. On another occasion the same animal accidentally received an overdose of sodium pentobarbital in preparation for angiography studies and survived after vigorous picrotoxin administration.

Function tests were performed 28 to 38 months later and included specific gravity and blood urea nitrogen determinations, response to water-loading, phenolsulfonphthalein excretion, and clearance studies.

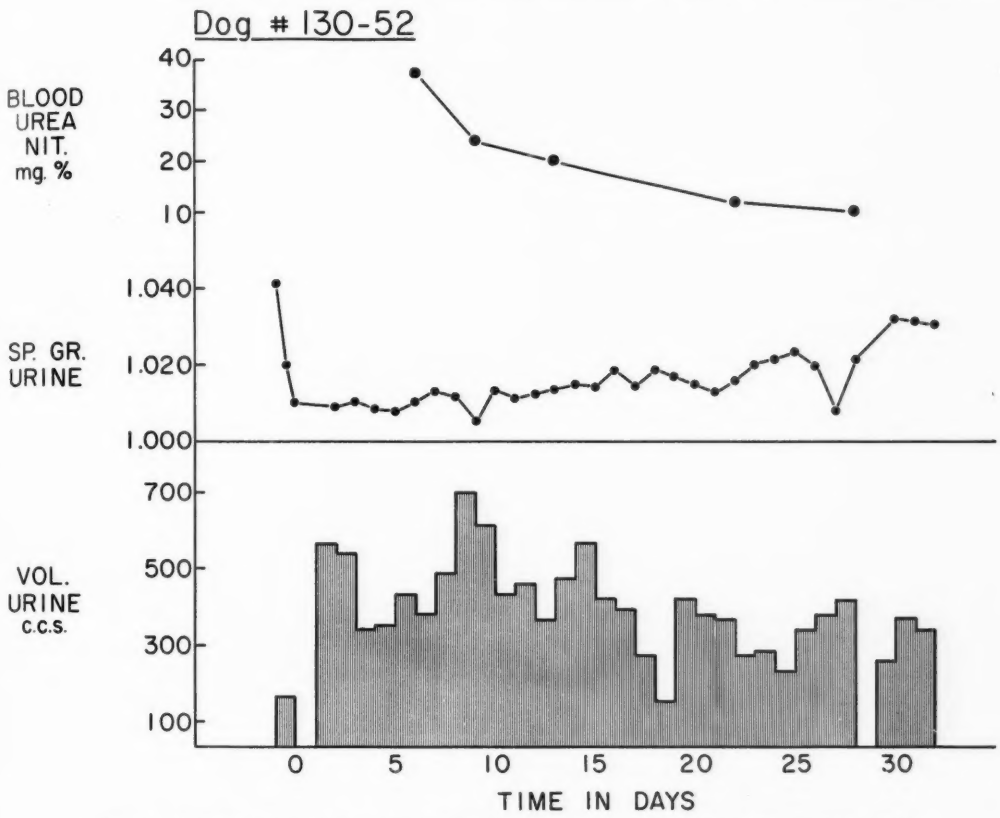


FIG. 1. A typical response of a dog to autotransplantation of one kidney after removal of the opposite kidney. Note the return to normal of the blood urea nitrogen, specific gravity, and the urine volume.

The highest specific gravities recorded as random observations on catheterized specimens were 1.060, 1.036, and 1.044. After 12 hour water deprivation the highest specific gravities were 1.058, 1.021, and 1.033 in each of the 3 dogs respectively. These data are shown in Table I.

The normal fasting blood urea nitrogen level of a normal two kidney dog in this laboratory is 9 to 14 milligrams per cent. Two of the present animals showed normal levels and the third showed a slight elevation of 20 milligram per cent (Table I).

After a water load of 30 cubic centimeters per kilogram of body weight by stomach tube in each of these animals the diuretic response was comparable to a two kidney dog with normal renal function. The pattern of water excretion for the autografted animals (Fig. 2) parallels almost exactly that of the controls (Fig. 3).

Table II shows the results of phenolsulfonphthalein (PSP) excretion in 2 normal animals as compared with the 3 animals with single autotransplanted kidneys. Three separate determinations were completed for each animal and no significant differences can be detected between the two groups.

Inulin clearance studies were performed to determine the glomerular filtration rate and para-aminohippuric acid (PAH) clearance studies to determine renal plasma flow. Standard clearance procedures were used and clearance observation periods of 15 to

TABLE II.—PHENOSULFONPHTHALEIN EXCRETION FROM AUTOLOGOUSLY TRANSPLANTED KIDNEYS AS COMPARED TO NORMAL KIDNEYS

	Experiment		
Dog	*1—per cent*	*2—per cent*	*3—per cent*
	NORMALS		
15-54	19.5 per 15 min.	19.0	20.0
	32.5 per 30 min.	30.0	32.0
235-53	34.4 per 15 min.	30.0	34.0
	50.4 per 30 min.	46.5	53.0
	TRANSPLANTS		
2-52	19.0 per 15 min.	19.5	22.5
	27.0 per 30 min.	27.5	33.5
130-52	30.0 per 15 min.	17.5	23.0
	53.0 per 30 min.	28.5	34.0
141-52	18.0 per 15 min.	18.5	18.0
	31.0 per 30 min.	29.5	34.0

20 minutes were obtained with each dog. The animals, studied without anesthesia, were given 30 cubic centimeters of water per kilogram through a stomach tube approximately 40 to 60 minutes prior to the first period of urine collection. The control clearance data, 3.84 cubic centimeters per kilogram per minute for inulin and 12.5 cubic centimeters per kilogram per minute for PAH, were obtained from the studies of Smith on normal, two kidney dogs.

The observed values on present dogs are tabulated in Table III. The inulin clearance values of 2.3 cubic centimeters for dog 2-52, 3.3 and 3.5 cubic centimeters for dog 130-52, and 2.5 cubic centimeters for dog 141-52 average to 76 per cent of the control value for two kidney dogs. The figures for PAH clearance of 8.1, 10.8, and 10.1 cubic centimeters respectively average to 78 per cent of the control values.

POSTMORTEM EXAMINATION

The animals were sacrificed 28 to 38 months after transplantation. The autotransplants of dogs 130-52 and 2-52 had increased an estimated 60 per cent in size (Fig. 4). The capsules were thin and translucent with no irregularities of the subcapsular cortex. The cut surface showed normal cortical and medullary architecture but the ratio of cortical to medullary width was increased over the normal by approximately 50 per cent. There was no evidence of pyelitis or pyelonephritis.

TABLE III.—CLEARANCE STUDIES ON AUTOTRANSPLANTED LIFE-SUSTAINING KIDNEYS IN DOGS

Dog	*Date*	**Inulin, c.c./kgm./min.*	†*PAH c.c./kgm./min.*
2-52	3-12-54	2.3	8.1
130-52	1- 5-54	3.3	
	3-15-54	3.5	10.8
141-52	3- 8-54	2.5	10.1

*Glomerular infiltration rate.
†Renal plasma flow.

Representative portions of each kidney were fixed in Bouin's solution or buffered 10 per cent formalin. Tissue sections were cut at 4 microns to permit detailed study of the basement membranes and cellularity of the glomerular and tubular portions of the nephrons. Hematoxylin and eosin and periodic acid-Schiff stains were performed on alternate serial sections.

Microscopically, in dog 130-52, the capsule was smooth, of normal thickness and cellularity, and there were no extensions of capsular connective tissue into the cortex. The interstitial tissue was normal, contained no excess of connective tissue, and there was no cellular infiltration. The glomeruli appeared uniform in size, vascularity, and cellularity (Fig. 5). There was a slight irregular thickening of the basement membrane of Bowman's capsule. The basement membrane of the glomerular tuft was normal. At the hilum there was a slight increase in periodic acid-Schiff material and in cellularity. The nuclei of these cells resembled those of smooth muscle and endothelial cells.

The glomerular tufts which showed some portion of the hilum were measured with a micrometer. The largest diameter only of each tuft was measured. The average diameter was almost one-third larger than the diameters obtained in 3 normal dog kidneys, which averaged 119 microns.

The tubules in both the cortex and medulla had normal epithelium and basement membranes (Fig. 6).

The arterioles and arteries were normal in size and cellularity. The juxtaglomerular body was not prominent and there were no granules in the wall of the afferent arteriole. The pelvic mucosa was normal.

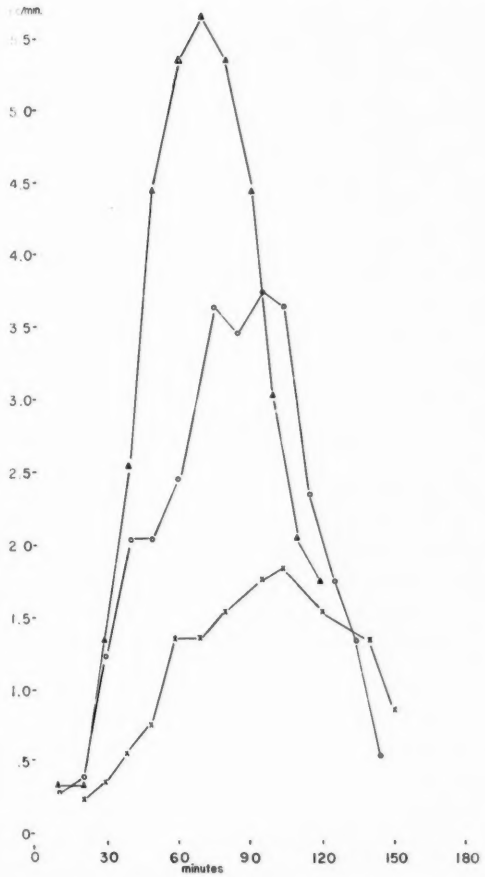


FIG. 2. Response to water load (30 c.c./kgm. of body weight by stomach tube) in 3 autotransplanted, single kidney dogs. Each point on the graph represents the average of 3 separate experiments.

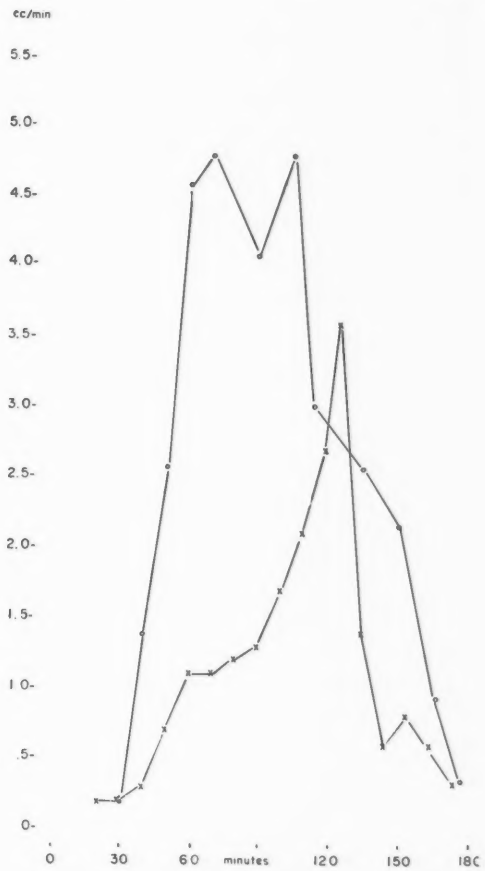
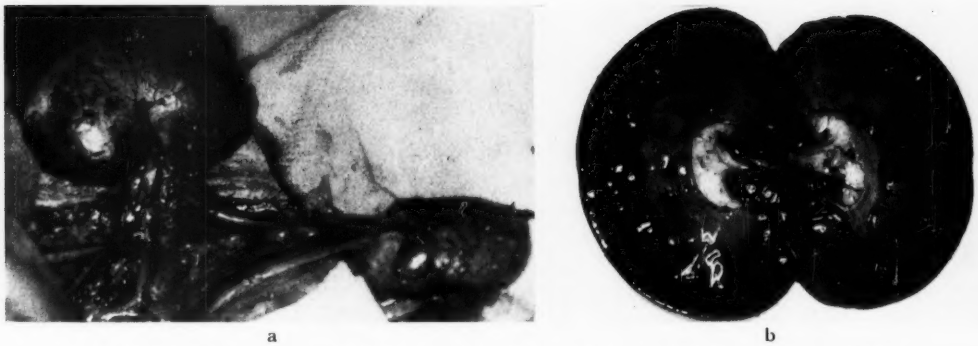


FIG. 3. Response to water load (30 c.c./kgm. of body weight by stomach tube) in 2 normal, two kidney dogs. Each point on the graph represents the average of 3 separate experiments.

The vascular anastomoses showed no cellular reaction except for slight intimal thickening at the arterial anastomosis. The nerves adjacent to the intact portions of the vessels (iliac artery and vein) appeared normal, whereas the nerves on the autotransplant side of the vascular anastomoses showed a cellular infiltration suggesting degeneration. Except for a slight increase in submucosal collagen with several foci of bone formation, the urinary bladder was normal.

In dog 2-52 the nerves in the autotransplant side of the anastomosis had increased cellularity and hyalinized foci, suggesting, as in dog 130-52, neural degeneration. Nerves adjacent to the iliac vessels appeared normal. The arteries and veins on either side of the anastomoses were intact and showed normal structure. The ureter and bladder also were normal except for slight chronic cystitis. The average diameter of the glomerular tuft was 160 microns, representing again an increased diameter of approximately one-third over that measurement which was obtained in the normal control dogs.



a b

FIG. 4. Gross appearance of life-sustaining renal autograft removed 2½ years after transplantation. The appearance is indistinguishable from that of a normal kidney which has undergone compensatory hypertrophy. a, Kidney in situ; b, cut surface.

DISCUSSION

Operative technique. The site of implantation, the avoidance of a skin ureterostomy, lack of movement of the kidney, and gravity drainage of the ureter apparently account for the prolonged normal function in these autotransplants.

The influence of environmental temperature on organ function is well known. Impaired spermatogenesis in an undescended testicle is an example. Possibly there is a deleterious effect on the transplant of the lower temperature in the subcutaneous tissues of a dog's neck. The pelvic area having the same environment as the renal fossa eliminates the temperature differential.

Avoidance of a cutaneous ureterostomy is desirable because of the probability of subsequent infection and pyelonephritis. Use of the renal fossa site requires either a cutaneous ureterostomy or a ureteroureteral anastomosis because the segment of transplanted ureter vascularized via the renal pedicle is too short to reach the bladder. The probability of stricture formation following this ureteral anastomosis precludes its use.

The pelvic area is the optimal site for several reasons: the iliac and renal vessels have nearly similar luminal size, the thermal and other environmental factors simulate those of the natural habitat of the kidney, the urinary bladder is close enough to allow direct implantation of the short segment of ureter, drainage is by gravity, and a cutaneous ureterostomy is avoided. The transplant can be easily fixed to the peritoneum, and the vessels and the ureter fall smoothly into place.

Perfusion of the kidney with heparin, saline, antibiotic, or other solutions is not only unnecessary but is actually detrimental for optimal functional recovery. Early in this study these substances were injected through the renal artery with the kidney in situ after dividing the renal vein. Possibly some of the impaired function resulted from the manual pressure exerted during the perfusion.

Splinting of the ureterovesical anastomotic site was not necessary. The presence of a foreign body traversing the site of healing between two normal well vascularized structures seemed undesirable. The problems of wound healing and of prophylaxis against stricture formation differed markedly from the usual clinical situations requiring the splinting of such anastomoses.

Postoperative observation and function tests. No difference between these animals and normal ones could be detected by observation. The animals gained weight, were alert, responded to stress, and withstood infection in a normal fashion. They were indistinguishable from the normal animal colony.

The ability of these animals to concentrate urine was unimpaired. Moreover, they

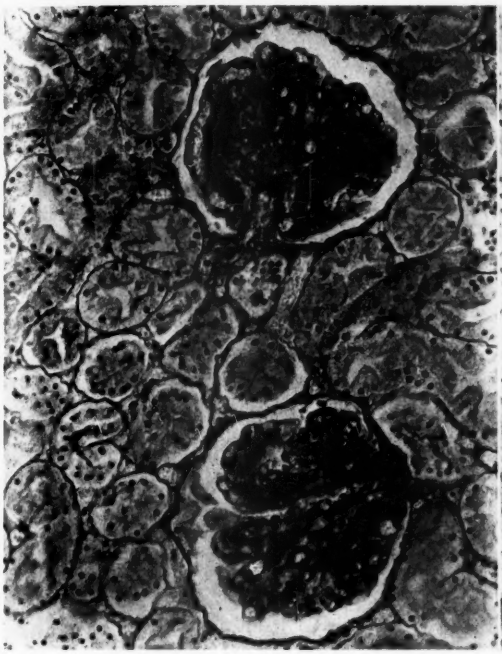


FIG. 5.

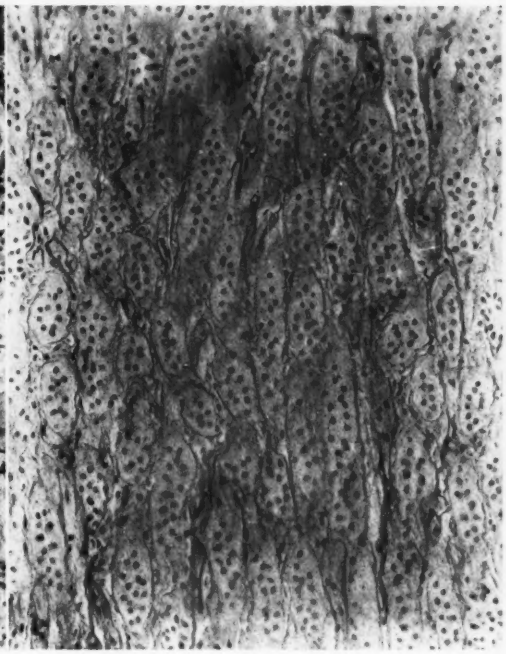


FIG. 6.

FIG. 5. Microscopic appearance of the cortex (dog 130-52) showing normal glomeruli 2 years after autotransplantation. ×271.

FIG. 6. Microscopic appearance of medulla (dog 2-52) showing normal tubules 38 months after transplantation. ×271.

responded in a normal manner to water-loading and to the PSP excretion tests.

The evidence of normal renal function in these single autotransplanted kidneys is noted in glomerular filtration rates and renal plasma flows which approach to 76 and 78 per cent the value seen in two kidney dogs with normal renal function. These data are remarkably similar to clearance studies in the case of a human kidney transplanted from one to the other of identical twins (5, 7). The recipient site selected in the transplantation of a human kidney was the same as that used in these experiments. The data from these experiments, which were available prior to the human twin transplantation, justified such a procedure after genetic identity had been established.

Postmortem examination. The objective evidence for the increased size of the autotransplanted kidney functioning as the only kidney over a long period was mentioned before. The external size was estimated to have increased by 60 per cent and the cortex by 50 per cent. The glomeruli by micrometer measurement were shown to be one-third larger than normal according to a comparison with measurements carried out in a similar manner on control kidneys. According to the data in Kunkel's study, the glomeruli in dogs of the size used in this study can be expected to have an average diameter of approximately 110 microns. Using this figure, the glomeruli in the autotransplants with average diameters of 158 and 160 microns would be 45 per cent larger than glomeruli in normal dogs of this weight. We (2) have observed a comparable increase in glomerular size without an increase in kidney size following prolonged neurogenic hypertension in the dog; the increase in glomerular size was considered to

be on a compensatory basis and related to focal glomerular impairment secondary to arteriosclerosis.

The nerves observed microscopically on the autotransplant side of the anastomosis in both kidney autotransplants showed cellular infiltration or focal hyalinization suggesting absence of regeneration, and it can be presumed that, even as denervated kidneys, these autotransplants manifested essentially normal function.

CONCLUSION

A life-sustaining autotransplant in a dog can function normally for at least 2½ years and persumably for the duration of a dog's life. The dogs seem normal in every way, feeding, running, sustaining pregnancy, and reacting to serious stress. The responses to water-loading, quantitative blood urea nitrogen determinations, PSP tests, and inulin and PAH clearance studies fail to reveal any abnormalities and suggest a marked degree of compensatory hypertrophy. At postmortem examination the autotransplant is observed to be increased in size, with an increased cortical width, and with glomeruli one-third to one-half larger than normal. There is absence of nerve regeneration in the autotransplant.

The act of transplantation does not prevent or compromise the ability of a kidney to hypertrophy. A transplanted kidney may function and sustain life as effectively as one kidney in its natural anatomic position. The data from these animals are surprisingly similar to those noted in a human homotransplant carried out between identical twins.

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BENIGN TUMORS OF THE LIVER

I. Adenomas

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THE NUMBER OF REPORTED CASES of successfully removed primary tumors of the liver is steadily increasing, and several excellent articles have described the various surgical methods that have been used. Resection of large portions of the liver, however, still remains a formidable procedure and ill advised attempts to remove some tumors may be extremely hazardous. The surgeon, therefore, must have a fundamental knowledge of the pathologic processes in the liver in order to decide which tumors require resection, which may respond to irradiation, and which, if any, may possibly be left alone with safety.

It is the purpose of this article and the succeeding articles in our series to review the surgical material available at the Mayo Clinic, to correlate the clinical and pathologic characteristics of primary benign hepatic tumors, and to evaluate the surgical experience with these tumors in an effort to improve the understanding of their management.

MATERIALS AND METHODS

This study is based on all cases of primary benign tumors of the liver of which records could be found in the surgical files of the Mayo Clinic between 1907 and 1954, inclusive, and in which satisfactory tissues or sections were available for histologic study. The clinical records in these cases were reviewed and the pertinent clinical and laboratory findings were recorded.

The gross specimens were then studied and sections were cut and stained with hematoxylin and eosin for histopathologic examination. The tumors were classified according to the following scheme:

CLASSIFICATION OF PRIMARY BENIGN TUMORS OF THE LIVER

I. Parenchymal tumors
   1. Hepatic cell adenomas (hepatoadenomas)
   2. Bile duct adenomas (cholangioadenomas)
   3. Mixed hepatic cell and bile duct adenomas (cholangeiohepatoadenomas, hamartomas)

II. Vascular tumors (hemangiomas, lymphangiomas)

III. Cysts
   1. Congenital
      a. Solitary unilocular cysts
      b. Diffuse polycystic disease
   2. Traumatic
   3. Inflammatory (specific, nonspecific)
   4. Neoplastic (cystadenomas, dermoids, cystic teratomas)
   5. Parasitic

IV. Others (fibromas, lipomas, leiomyomas, teratomas, adrenal rests)

The complete study comprised 13 benign adenomas, 35 hemangiomas, and 76 nonparasitic cysts; of the last-named group, 29 lesions were examples of polycystic disease, 38 were solitary cysts, 5 were multilocular cystadenomas, and 4 were traumatic cysts. The present report will be confined to a consideration of benign hepatic adenomas.

REVIEW OF THE LITERATURE

Frerichs, in 1861, said that some neoplasms of the liver were of slight importance since they were attended by scarcely any constitutional symptoms. He placed cavern-

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Abridgment of portion of thesis submitted by Dr. Henson to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

Dr. Howard K. Gray now deceased.

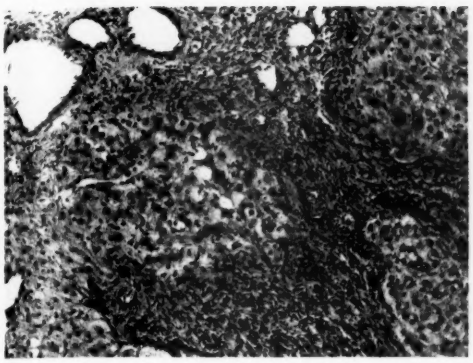
TABLE I.—SUMMARY OF DATA IN 4 HEPATOADENOMAS AND 2 CHOLANGIOHEPATOADENOMAS

		Clinical features					*Lesion*		
Tumor, type	*Case*	*Age, yrs.*	*Sex*	*Chief complaint*	*Duration of symptoms*	*Roentgenologic findings*	*Size, cm.*	*Site, lobe*	*Follow-up, years*
Hepatoadenoma	1	5	F	Mass	1 mo.	—	15	R	4?
	2	28	F	Pain, mass	1 yr.	Mass displacing stomach	6	L	2
	3	39	F	Duodenal ulcer	—	—	10; multiple	R and L	2
	4	64	M	Gallstones	—	—	4	R	3½
Cholangiohepato-adenoma (hamartoma)	5	12/12	M	Mass	5 mos.	Mass, elevated diaphragm	15	R	Died 2 hours after operation
	6	10/12	M	Large liver	1 mo.	Extrarenal mass, elevated diaphragm	20	R	1½

ous tumors and tubercles in this category. Virchow differentiated primary hepatic tumors from the commoner secondary neoplasms and Witwicky, in 1899, classified primary hepatic tumors by dividing them into those originating from hepatic cells, those springing from bile ducts, and a mixed group that exhibited both hepatic cells and bile duct epithelium. Warvi (17, 18) recently modified this classification to include other tumors that are primary in the liver but not of parenchymal origin.

Because of the remarkable ability of the liver to regenerate itself, it is often difficult to decide whether a given tumor is hyperplastic or neoplastic, and separation of benign adenomas from potentially malignant growths may be almost impossible. Simmonds, in 1884, reported a localized hyperplastic nodule that he considered to be a response by the liver to injury but suggested the possibility of its congenital origin. Witwicky thought that adenomas of the liver developed on the basis of cirrhosis and that hyperplastic nodules were but an intermediate step in the process. Albrecht, in 1904, suggested the term "hamartoma," which by definition is a tumor-like formation of congenital origin. More recently, Stewart and associates reviewed a great deal of experimental and veterinary literature in an effort to explain the cause of such nodules in otherwise noncirrhotic livers. They used the term "focal cirrhosis" and cited evidence suggesting that physical stresses on localized regions of hepatic tissue by the ligaments and capsule might be of etiologic significance. Benz and Baggenstoss recently discussed the relationship between focal cirrhosis and hamartomas. That such localized zones may result from injury is well known; several authors have suggested that a predisposition to injury may result from congenital aberrant vessels or biliary channels. Ewing summarized these views and discussed the relationship of hyperplasia to neoplasia.

The first important contribution concerning the surgical management of hepatic tumors was by Keen (5), in 1892, who found reports of 20 cases in the literature in which resection of the liver had been accomplished. He credited Langenbuch as being the first to report a case (1888) and Tiffany as being the first American surgeon to do so (1890). Keen (6) later was able to find records of 76 hepatic tumors that had been resected, with a mortality rate of 14.9 per cent. The Tinkers, in 1939, reviewed the pertinent experimental work that had been reported on resection of the liver and stated that the average busy surgeon probably would be faced with the problem of resecting a hepatic tumor at least once during his practice. Warvi (17, 18) summarized the various technical considerations in partial hepatectomy and found a total of 570 reported cases, 223 of which included descriptions of the operation and the microscopic diagnosis. Quattlebaum and Stone and Saypol recently have reviewed material concerning partial hepatectomy for various benign and malig-



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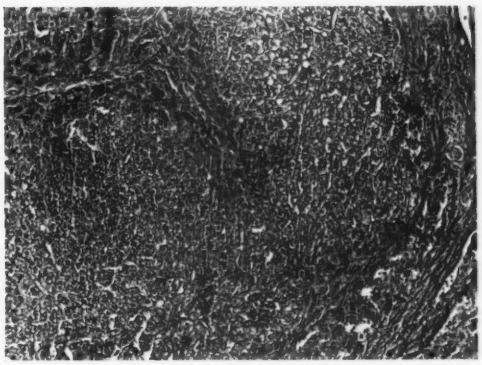


b

FIG. 1. Hepatoadenomas. a, Regenerative hyperplasia illustrating extremely active proliferation of hepatic cells divided into nodules by fibrous tissue septa, proliferation of bile ducts and cellular infiltration. The tumor was an irregular 4 centimeter mass projecting from the free edge of the liver. The remainder of the liver was normal. This is probably an example of postnecrotic cirrhosis, although the past history was negative, and the tumor was an incidental finding during operation. b, Section from a regenerative tumor 15 centimeters in diameter illustrating condensation of hepatic elements to form a pseudocapsule. Both, hematoxylin and eosin, ×74.

nant conditions, including metastatic carcinoma.

HEPATOADENOMAS

Benign tumors originating from hepatic cells are rare unless examples of localized hyperplasia are included. These so-called regenerative nodules are usually small and asymptomatic, being seen not uncommonly at necropsy or as an incidental finding at operation. Occasionally, however, they attain sufficient size to be surgically significant, and the surgeon is faced with the problem of deciding what they are and how to deal with them.

Four such tumors were present in our series of patients (Table I). Two of the patients underwent exploration because they complained of an abdominal mass, and 2 were found to have hepatic tumors at operation for another condition. One of the former 2 patients had noticed the mass during an episode of abdominal pain associated with chills and fever, whereas the second had complained of intermittent crampy abdominal pain for a year. The third patient had a subtotal gastric resection for duodenal ulcer and the fourth had a cholecystectomy for cholelithiasis.

These tumors were firm, irregularly rounded, and dark red. They varied from 4 to 15 centimeters in diameter, with an average of 9 centimeters. One patient had multiple tumors the size of a fist occupying both lobes. The cut surfaces of these 4 tumors showed them to be divided into irregular lobules by bands of fibrous tissue that was densest near the center. They appeared grossly to be encapsulated, with a narrow rim of connective tissue separating the tumor from the adjoining parenchyma.

Histologically, the tumors showed nodular hyperplasia and fibrosis. The hepatic cells tended to be arranged in lobules that were divided irregularly into smaller nodules and isolated cords by bands of fibrous tissue. Proliferation of bile ducts was present, accompanied in some zones by dilatation of blood vessels and infiltration with lymphocytes. Active proliferation of parenchymal cells was pronounced in some instances, with variation in size of the hepatic cells as well as in their size and the number of nuclei (Fig. 1a). The surrounding parenchyma tended to be compressed into a pseudocapsule (Fig. 1b).

The tumor was excised completely in 3 instances, whereas biopsy only was accom-

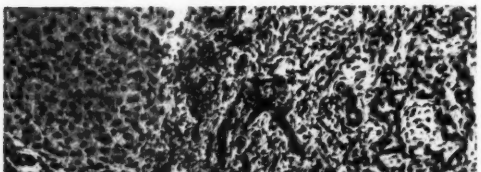


FIG. 2. Cholangioadenoma of the liver showing proliferation of bile ducts, increase of connective tissue, and infiltration with lymphocytes. Normal hepatic cells are shown in the upper left corner. Hematoxylin and eosin, ×107.

plished in the patient who had multiple tumors involving both lobes. All 4 patients had an uneventful convalescence and have had no further difficulty. They have been observed for periods of from 2 to 47 years. Of special interest is the patient whose tumors were not removed; she has been followed for 2 years without evidence of progression in size of the tumors and with absence of symptoms.

CHOLANGIOADENOMAS

Cholangiomas are primary hepatic tumors of bile duct origin. This designation, like hepatoma, is general in nature and does not indicate the benignancy or malignancy of the tumor. Cholangioadenoma and cholangiocarcinoma are more specific terms and are to be preferred, since they designate not only the origin of the tumor but also the growth potential of the predominant type of cell.

Seven patients in our series had primary benign hepatic tumors originating from the bile ducts. These lesions are not included in Table I because they are small and are important only because they may be mistaken for metastatic malignant tumors. Four of the patients were women and 3 were men; the average age was 54 years, the youngest being 38 and the oldest 69. These tumors did not produce any signs or symptoms, and all of them were found incidentally at operation. Three of the patients were operated upon for gallstones, 2 had carcinoma of the stomach, and 1 had carcinoma of the pancreas. The seventh patient was operated on because of persistent vague abdominal complaints, the cause of which was not determined at the time of operation.

The tumors were all small; the largest was 1.5 centimeters in diameter and the smallest measured 0.3 centimeter. They were described grossly by the surgeon as a small nodule in 3 instances and as a subcapsular plaque, a metastatic area, a cystic area, and simply a small tumor in 1 instance each. They occupied a subcapsular position in each patient and usually were excised as material for biopsy to rule out metastatic carcinoma.

Histologically, these tumors consisted of small islands of proliferating bile duct epithelium arranged in cords or tubules that were separated by varying amounts of fibrous connective tissue (Fig. 2). Rather pronounced infiltration by lymphocytes was present in some regions. A definite capsule was absent and the adjacent parenchyma appeared normal in most instances.

CHOLANGIOHEPATOADENOMAS

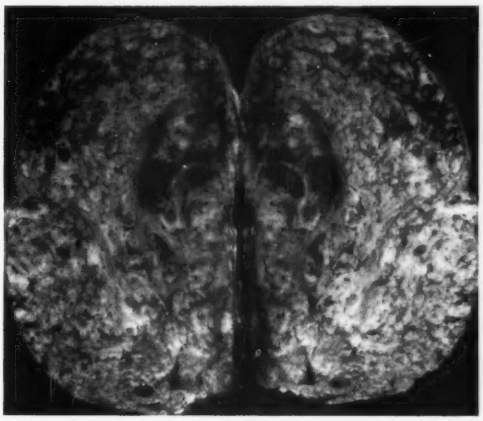
Almost all parenchymal tumors of the liver show varying amounts of hyperplasia of hepatic cells and proliferation of bile ducts. One attempts to classify them according to the predominant type of cell. In some instances, however, the hyperplastic process involves both elements and the picture may be complicated further in that the amount of connective tissue may be increased to such an extent that it is the dominant feature of the tumor. The tumors comprising this mixed group are called cholangiohepatoadenomas, and the category includes a controversial group of tumors called hamartomas. The problem of differentiating hamartomas from other parenchymal tumors of the liver has been considered extensively in the literature.

There were 2 male infants with so-called hamartomas of the liver in the present series (Table I). One was 14 months of age and the other was 10 months of age. Each had had a normal birth and development, and neither had had any serious illness. The abdomen in 1 patient had been enlarging gradually for 5 months, whereas abdominal enlargement of 1 month's duration had been present in the other patient. An abdominal mass had been discovered recently in both. The first baby had been given a course of roentgen therapy in an effort to reduce the size of the tumor but without success.

Examination of each child disclosed a large, smooth mass filling the entire right side of the abdomen and extending below and to the left of the umbilicus. The mass was slightly tender in 1 patient.

At operation, each patient had a huge tumor that almost completely replaced the right lobe of the liver. The neoplasm in the first patient was a reddish-brown, fairly well delineated, firm, smooth, solid mass that measured 15 by 10 by 10 centimeters (Fig. 3a). The cut surface showed the tissue to be encapsulated, firm, and rubbery, with alternating zones of hepatic tissue and thick bands of connective tissue. Large septa of fibrous tissue ran through the tumor, and several zones of cystic degeneration were noted. The tumor in the second patient was a huge, multilocular, cystic mass about 20 centimeters in diameter involving the right lobe of the liver. It displaced the medial portion of the right lobe and all of the left lobe far into the left side of the abdomen.

These 2 tumors presented a similar histologic appearance, consisting of islands of hepatic cells interspersed between broad zones of connective tissue containing numerous proliferating bile ducts and dilated vascular channels (Fig. 3b). The hepatic cells appeared to be entirely normal in some regions, whereas they were small and compressed by the fibrous tissue in other parts and hyperplastic in still other zones. The proliferating bile ducts were dilated and distorted by the greatly increased fibrous tissue, and mild to moderate infiltration by lymphocytes was noted in some parts. A striking feature of these tumors was the complete disorganization of hepatic elements.



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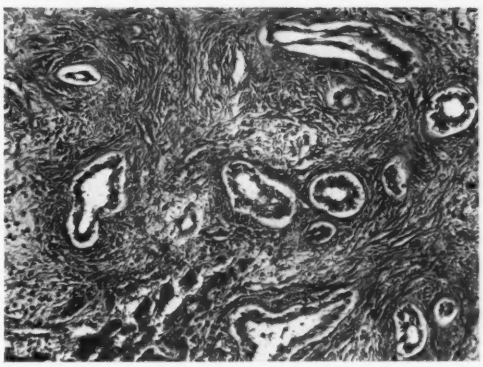

b

FIG. 3. Case 5. Cholangiohepatoadenoma (hamartoma) of liver. a, Gross appearance of the encapsulated, firm, fibrous tumor measuring 15 by 10 centimeters. Note the thick bands of fibrous tissue and the cystic necrotic zones. b, Histologic appearance of same tumor. Note the disorganized hepatic elements scattered through broad zones of connective tissue, with proliferation of bile ducts, islands of parenchymal cells, and mild cellular infiltration. Hematoxylin and eosin, ×89.

The tumor was excised in both instances. Cardiac arrest developed in the first child during the course of the operation and it was necessary to open the thorax and massage the heart. Normal rhythm was re-established and the operation was completed rapidly but the patient died 2 hours after

operation. In the second patient, the cyst was aspirated first and then was excised, along with approximately two-thirds of the right lobe of the liver. A portion of the wall of the cyst lying near the inferior vena cava was not removed but was obliterated by the suture. This patient has been followed for 1½ years and is well and active, without evidence of recurrence.

PREOPERATIVE DIAGNOSIS

In only 4 of these 13 patients with hepatic adenomas was the surgical exploration done because of clinical manifestations thought to be caused by the tumor. Determination of serum bilirubin was done in 2 instances and a sulfobromophthalein test in 1; the results showed no significant abnormalities. Roentgenograms of the abdomen showed a large soft tissue mass with elevation of the diaphragm in 3 patients, in 1 of whom persistent deformity of the stomach was demonstrated by means of ingestion of barium.

The preoperative diagnosis in all 4 of the patients was an indeterminate abdominal mass, hepatic tumor being suggested in 2. Wilms's tumor, neuroblastoma, and retroperitoneal tumor were considered in the differential diagnosis.

COMMENT

It appears to be well established that localized hyperplasia of the liver occurs and that this process may progress to the formation of large solitary tumors. The cause of such a process is not usually clear, however, and whether it is the result of local injury (focal cirrhosis) or a congenital abnormality (hamartoma) is unlikely to be proved except in an occasional case.

Mann showed that the liver of the dog has remarkable powers of regeneration as long as the portal blood flow is not impaired. His experiments also demonstrated that the weight of regenerated hepatic tissue after partial hepatectomy may exceed that of the tissue excised. He further pointed out that nodular regeneration is a self-limiting process, since the nodules themselves progressively interfere with the portal blood flow. It is probable, therefore, that the portal blood supply in an occasional case remains adequate in the face of continuing stimulation until nodular regeneration progresses to the formation of large localized tumors.

That hyperplastic cells may undergo transformation into neoplastic cells has been clearly shown and is characteristic of many neoplastic processes. The great incidence of cirrhosis in primary tumors of the liver and the uniform gradation among nodular hyperplasia, multiple adenomas, and multiple carcinomas certainly favor such a view. For this reason, most surgeons have recommended excision of such tumors as the treatment of choice. On the other hand, many of the reported deaths have occurred as a result of attempted excision of hepatic tumors; the fact that 1 of our patients has remained well without symptoms or evidence of progression in size of multiple tumors that were left in the liver suggests a more conservative attitude. If the diagnosis of a regenerative tumor can be definitely established at operation, or if conditions for excision of the tumor are not favorable, it is probably better to remove material for biopsy and close the abdomen rather than subject the patient to a long hazardous procedure. If histologic study of the tissue suggests that the lesion is malignant, a second operation under more favorable circumstances can be accomplished.

Benz and Baggenstoss pointed out two factors of surgical importance regarding small nodular proliferations in the liver: (1) because these small nodules may be mistaken at laparotomy for metastatic carcinoma, their identity should be proved by biopsy in all cases and (2) because most of these lesions lack a true capsule, removal of the nodular mass by shelling it out may leave nodules of regeneration behind.

As mentioned previously, Albrecht introduced the term hamartoma to designate a tumor-like malformation containing an abnormal mixture of normal constituents of an

organ, whether it be in amount, arrangement, or degree of maturation, or in all these respects. Hamartomas of the liver are thought to be true congenital aberrations of growth and are found more frequently in children than in adults. Several investigators have suggested that congenital abnormalities of the vessels or bile ducts may stimulate growth of tumors late in adult life. The 2 tumors in our series described in the section on cholangiohepatoadenomas are thought to fulfill the criteria of hamartomas as described in the literature. The ages of the patients, the large size of the tumors, the continued growth, the remarkably hyperplastic fibrous tissue, and the encapsulation all tend to favor this view. The fibrous tissue in these tumors is not condensation of hepatic elements, as seen in regenerative nodules, but consists of broad bands and islands of hyperplastic connective tissue surrounding and distorting the proliferating bile ducts. The picture is similar to that seen in pericanalicular fibroadenoma of the breast, as pointed out by Lee.

Experience with this type of tumor is limited but, because of the progression in size, the growth potential with the possibility of malignant transformation, and the danger of hemorrhage or of twisting if it is on a pedicle, it is our opinion that such lesions should be excised. This view is shared by the majority of writers.

SUMMARY AND CONCLUSIONS

A review has been made of the records of 13 patients with benign adenomas of the liver seen at the Mayo Clinic from 1907 to 1954, inclusive. The tumors were classified histologically into 3 groups according to the predominant type of cell.

Hepatoadenomas, the first group, are tumors composed of hepatic cells. Included are localized nodules of regenerative hyperplasia that have progressed to the formation of large tumors. They are distinguishable from hamartomas, with which they sometimes are confused, and probably require no treatment, although this has not been proved. Four large tumors of this type were included in the series.

Cholangioadenomas, the second group, are tumors originating from bile ducts, usually in the form of small subcapsular collections of proliferating bile duct epithelium. They are commonly found at necropsy and are considered important because the surgeon must realize that they can simulate closely a metastatic deposit and, therefore, one should not assume that these small nodules are malignant until such is proved by biopsy. Seven such tumors were included.

Cholangiohepatoadenomas, the third group, are mixed tumors originating from both hepatic cells and bile ducts. Two tumors of this type were included. Such lesions show pronounced hyperplasia of the connective tissue elements. These 2 tumors were similar to many that have been reported in the literature as hamartomas. They occur more frequently in infants than in adults and may grow to large size. They may be cystic or solid and usually are found in the right lobe. They should be excised if it is possible to do so.

Four of these 13 patients underwent surgical exploration because of clinical manifestations thought to be caused by the hepatic tumor. These manifestations consisted of gradual enlargement of the abdomen, the discovery of an abdominal mass, or the presence of intermittent abdominal pain. Examination disclosed a palpable mass in each of these patients. Roentgenograms showed a mass displacing the diaphragm or the adjacent viscera in 3 of these 4 patients. The preoperative diagnosis was an indeterminate abdominal mass in each instance, with hepatic tumor being suggested in 2 instances.

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AN EXPERIMENTAL STUDY OF THE DEGENERATION AND REGENERATION OF NERVE FIBERS FOLLOWING A BURN

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CORRECT EVALUATION of the extent and depth of burns is important in planning all phases of the treatment of a burned patient, and it is particularly critical during the time of skin coverage of severely injured areas. An accurate estimate of the extent of the injured surface is always possible, and it may sometimes be stated that a particular burn is first, second, or third degree in depth. However, differentiation between second and third degree burns quite often perplexes even the expert, and it is precisely this difference which means healing by time on the one hand and healing by grafting on the other. There are good reasons why this distinction is so difficult soon after injury. One reason is the variation in thickness of skin in different parts of the body. Another is the variation in the early appearance of flash burns, scalds, and contact burns. It is not until later that one sees the deep slough of the third degree burn or the welcome epithelium in the second degree burn and may classify with confidence the equivocal areas.

How long after a given burn these signs appear is a matter of debate, but there is general agreement that they will be present by at least the fourteenth to eighteenth day. However, earlier skin coverage of deeply burned areas has been increasingly stressed, and primary excision and grafting has attracted much attention. The advantages of primary or early grafting are obvious, but there is the disadvantage that too little or too much burned area may be so treated because of the difficulty in grading some second and third degree burns. One accepted aid to making this distinction is to test the sensitivity of the area; the belief is prevalent that an appreciation of pinprick means the burn is not of full thickness and that a loss of sensation indicates a deep second or third degree burn.

Since the ability to perceive painful stimuli in an injured area depends on functioning nerve fibers in that area, it would be of interest to determine the effects of burns on nerve fibers. This report is a study of the degeneration and regeneration of nerve fibers, at timed intervals, in an area subjected to one type of burn. Some observations on the ability of the experimental animal to react to pinpricks in the injured areas and on gross and other microscopic characteristics of these areas are included.

MATERIAL AND METHODS

Albino rabbits, weighing 2 to 4 pounds, were selected as the experimental animal. The nerve fibers in these animals can be displayed particularly well, and much is known about their peripheral neurohistology.

After preliminary work with other types and degrees of severity of burn, the following standard burn was chosen and is the one on which this study is based. A tungsten lamp source was used to produce a standard flash burn; 4.88 calories per square centimeter were delivered at an irradiance of 2.44 calories per square centimeter per second. This burn was delivered to the dorsum of the ear through a 16 millimeter port after both dorsal and ventral surfaces had been shaved. The skin of the dorsum of the ear, therefore, received an injury comparable to an ordinary radiant energy thermal burn, but the ventral skin suffered an unusual type of damage as the deeper layers received more energy than the superficial layers.

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TABLE I.—SUMMARY OF RESULTS

Time after burn	*Gross appearance*	*Microscopic evaluation of innervation*	*Area of absence of pinprick*
First 10 min.	Erythema which fades as edema develops	—	—
45 to 60 mins.	Edema	Superficial nerve fibers absent in the central area. Damaged nerve fibers present	
4 hrs.	Deep erythema, *8 to 9 mm.	Absence of nerve fibers, *5 mm.	—
	Slight edema, 15 to 16 mm. (total)	Decreased innervation, 1 to 1.5 mm. Fewer damaged fibers seen	5 mm.
18 to 24 hrs.	Cyanosis, 10 to 11 mm.	Absence of nerve fibers, 8 mm.	
	Induration, 14 to 16 mm. (total)	Damaged nerve fibers, 0.5 mm. Decreased innervation, 1.5 mm.	9 to 10 mm.
2 to 4 days	Central crust, 3 to 4 mm. Edema and cyanosis	Dorsal surface: Maximal damage Absence of innervation, 9 mm. Rare damaged fiber stained In the periphery, fewer dermal nerve fibers Ventral surface: Absence of innervation, 5 mm. Thinned innervation in periphery	9 to 10 mm.
2 wks.	Central slough, 2 to 3 mm. Hypertrophic scar, 2 to 4 mm. Thinner scar, 1 to 3 mm. Induration, 11 to 13 mm. (total)	Dorsal surface: No nerve fibers in the hypertrophic scar Reinnervation of periphery by isolated, single fibers Ventral surface: Little reinnervation	6 to 8 mm.
3 wks.	Slight contraction, otherwise as at 2 wks.	Scant reinnervation of hypertrophic scar. Good innervation in periphery	5 to 7 mm.
4 wks.	As at 2 and 3 wks.	Dorsal surface: Many nerve fibers in area of hypertrophic scar More small nerve trunks Ventral surface: Nearly normal	Sensation returned to hypertrophic scar
7 wks.	Hair growing in periphery of hypertrophic scar	Dorsal surface: Nearly normal innervation where hair follicles are numerous Decreased number of fibers per trunk centrally Ventral surface: Appears normally innervated up to the central slough	As at 4 wks.

*The first figure refers to the diameter of the central, most severely damaged area. Unless otherwise noted, the following figures refer to the width of a ring around this area, that is, the width from the nearest central zone to the next peripheral zone.

The technique of displaying the nerve fibers is merely another modification of one of the numerous methylene blue methods summarized by Weddell and Zander and also includes certain refinements on which the author and others have worked with Weddell (1). In the preliminary work it was found that this technique did not alter the appearance of normal nerve fibers, that it consistently displayed the fine nerve terminals, and that hyaluronidase aided in diffusing the dye.

Two and one-half cubic centimeters of a solution of 75 turbidity reducing units of hyaluronidase in 2.5 cubic centimeters of normal saline were injected through a No. 27 needle into the subcutaneous tissue of each ear. Thirty minutes later 4 cubic centimeters of 0.05 per cent methylene blue (0.1 per cent methylene blue in normal saline diluted with an equal part of 2 per cent procaine hydrochloride) were injected over a 1 minute period into a marginal vein of the ear. During the injection and for 30 seconds after its completion, the venous return was delayed by occlusion of the vessels near the base of the ear. Thirty to 45 minutes after staining, the full thickness of the skin was excised and placed in a cold, saturated solution of ammonium molybdate. In preparing tissues for study less than 1 hour after the burn, these times were modified, and hyaluronidase was often omitted altogether. Three drops of 1 per cent osmic acid were added to each 100 cubic centimeters of the molybdate solution just before the skin was

immersed. The tissue was refrigerated in molybdate for 24 hours, washed in running tap water for 1 hour, dehydrated in cold absolute alcohol, cleared in xylene, and stored in methyl salicylate.

The time between burning and staining the skin varied from a few minutes to 2 months. It is emphasized that the staining of the nerve fibers was carried out in the living animal, and that an area of normal skin surrounding and equal to or greater in size than the burned area was included with each specimen. Each burn, therefore, had its own control so that only those specimens showing complete staining in the normal areas would be used. It is also pointed out that this tissue is not sectioned. The whole preparation, after being cleared, is mounted in methyl salicylate for microscopic examination. It is thus possible to trace the pattern of innervation and to measure the relative areas of different degrees of damage. For each burn a piece of dorsal and a piece of ventral skin of the ear were examined.

The ability of an animal to respond to pinprick in the burned areas was tested with a N 24 needle. Absence of response was recorded only if the animal: (1) was not under anesthesia, (2) failed to respond to repeated stimuli, and (3) responded normally to pinprick in a nearby, undamaged area.

RESULTS

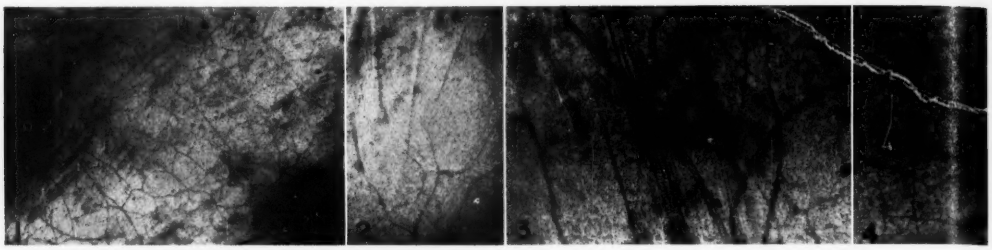
A summary of the results is presented in Table I. The observations are most easily detailed by presenting gross and microscopic appearance together and by separating them into postburn intervals. Unless otherwise noted, there is little difference between the dorsal and ventral skin except that, in general, the area of damage is slightly larger on the dorsal side of the ear. The time noted refers to the interval between burning and excising the skin. Staining of the nerve fibers has taken place during the preceding 30 to 45 minutes.

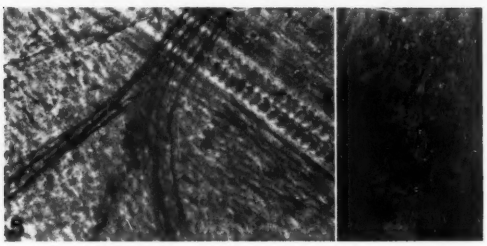
Figures 1 to 13 illustrate certain features of the neurohistology of normal and burned skin, and the descriptions which follow can be more clearly understood by reference to these illustrations. Figures 1 to 4 are various enlargements of the normal neural pattern in the skin of the rabbit's ear. Figure 5 shows a typical nerve trunk and Figure 6 depicts the "fine, beaded terminals" which will be mentioned later. Figures 7 and 8 are two different enlargements of the complex innervation of the base of a hair follicle. Figures 9 and 10 illustrate the changes in the neural pattern which occur at the periphery of a burn, and Figure 11 is an example of a small, dermal nerve trunk which persists in a burned area. Figures 12 and 13 illustrate the absence of nerve fibers in severely burned areas; the former also shows hyperemic engorgement of the small blood vessels.

First 10 minutes. When the dorsum of the rabbit's ear is exposed to radiant energy of 2.44 calories per square centimeter per second for 2 seconds, a faint erythema appears within a minute following the burn. Edema begins centrally and at first looks like a small blister, but this swelling gradually spreads so that in 10 minutes the entire exposed area is edematous. As edema develops erythema fades. Because of the length of time necessary to stain the nerve fibers, there are no microscopic observations at this period.

Forty-five to 60 minutes. Edema is still the most prominent feature of the burn. It is either confined to the exposed area or is spread only a little beyond it. Grossly, there is no obvious evidence of epithelial damage. The degree of hyperemia is variable.

The most striking microscopic feature is a complete absence of nerve fibers in the superficial layers of the burned skin of the central area of the dorsum of the ear. Beyond this central zone there is a general thinning of the innervation, and damaged, swollen fibers are seen. Some dermal nerve trunks are clearly stained and appear normal, but their number is decreased. On the ventral surface thinning of the nerve fibers is noted but is much less profound than in the skin of the dorsal surface of the ear. Some normal appearing nerve fibers





FIGS. 1 to 13. The neurohistology of normal and burned skin of the rabbit's ear. Vital methylene blue staining; full thickness preparations.

FIG. 1. Normal nerve fiber pattern. ×17.

FIG. 2. Normal nerve pattern. ×33.

FIG. 3. Normal nerve pattern of ventral surface. ×59.

FIG. 4. Small dermal nerve trunks of the dorsal surface. ×59.

FIG. 5. Normal nerve trunk. ×213.

FIG. 6. Fine, beaded nerve terminal in the epithelial layer. ×213.

are seen in an area which will eventually be a full thickness slough.

Four hours. Only a little edema remains in an area 15 to 16 millimeters in diameter. A central zone, 8 to 9 millimeters in diameter, of deep erythema has appeared. Microscopically, an 8 millimeter zone of marked hyperemia is present. Nerve fibers do not stain in the central 5 to 5.5 millimeter zone, and there is a marked decrease in the number of nerve fibers for a further 1 to 1.5 millimeters. Thus, erythema extends a short distance beyond the zone of marked neural damage. At this time very few damaged nerve fibers are seen and these are in a zone about 0.25 millimeter wide. Fibers seem either to be present and normal or to be absent, and in the normal appearing zone both superficial, beaded fibers, and deeper dermal fibers stain well. Four hours following the burn a nocifensive response cannot usually be obtained from an area 5 millimeters in diameter in the center of the burn.

Eighteen to 24 hours. The area of gross damage now varies from 14 to 16 millimeters on the dorsal surface. This consists of a slightly indurated, cyanotic area 10 to 11 millimeters in diameter surrounded by a zone of hyperemia. The ventral surface presents nearly the same appearance except that the cyanotic area is slightly smaller (1 to 2 millimeters) and hyperemia is less pronounced. There is no evidence of a char, crust, or slough at this time. There is complete absence of nerve fibers in a central zone 8 millimeters in diameter, and a few degenerating fibers stain in a zone 0.5 millimeter wide around this area. Beyond this there is a further area 1.5 millimeters wide in which the innervation is markedly decreased, and hyperemia is evident 2 millimeters beyond. Just peripheral to the area of complete absence of nerve fibers, an occasional, single deep dermal nerve fiber is seen in an area in which no superficial fibers appear. The area of absence of pinprick sensation has increased from 5 millimeters at 4 hours to 9 to 10 millimeters at 24 hours.

Two to 4 days. The burned area is edematous, cyanotic in the center, and hyperemic at the periphery. The zone of hyperemia is slightly narrower than at 24 hours, but the degree of hyperemia is greater. On the dorsum a 3 to 4 millimeter crust has formed. In the dorsal skin of the ear there is evidence of maximum neural damage at this time interval. There is complete absence of innervation in the central 9 millimeter area, and the rule now, with a rare exception, is

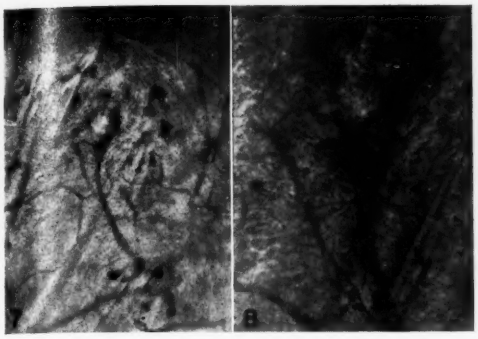


FIG. 7. Multiple innervation of a hair follicle. ×57.

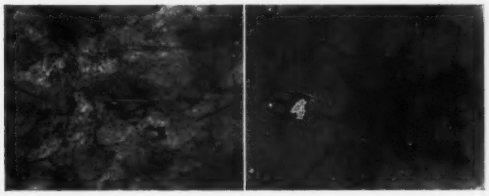


FIG. 8. Hair follicle innervation; accessory beaded fiber. ×213.

FIG. 9. The periphery of a burn 1 hour after exposure. Normal, dense innervation on the left. Thinned neural pattern on the right. ×15.

FIG. 10. The periphery of a burn 1 hour after exposure. Damaged nerve fibers on the left. Absence of nerve fibers on the right. ×52.

that a nerve fiber appears normal or does not take the stain at all. In the zone surrounding the central, complete damage, fewer dermal fibers are present than existed at 24 hours, but, particularly by the fourth day, some superficial, beaded fibers make their appearance. Thus, destruction has reached its height and reinnervation in the form of single, superficial fibers is just beginning. Damage has not progressed completely on the ventral surface. A central zone of 5 millimeters is devoid of innervation, but beyond this a number of superficial, beaded fibers are seen. At the periphery the deeper innervation is quite thinned in an area in which numerous superficial fibers appear. Occasionally, degenerating superficial fibers are also seen. Pinprick response still cannot be obtained from the central 9 to 10 millimeter area.

Two weeks. There has been a full thickness slough of dorsal skin, cartilage, and ventral skin from the ear and a 2 to 3 millimeter hole is present in the center of the exposed area. A 2 to 4 millimeter zone of reddish brown, hypertrophic scar covered with epithelium surrounds the hole. More peripherally there is a 1 to 3 millimeter zone of lighter colored scar with a narrow zone of pigmentation around it. The area of gross damage measures 11 to 13 millimeters. The area of dark, hypertrophic scar is devoid of nerve fibers. The lighter colored area presents many nerve fibers traveling alone rather than in small trunks. A number of superficial, beaded fibers branch frequently and cover rather wide areas. The isolated fiber is the rule here, and rarely is multiple innervation of a single area seen. The superficial fibers have made more progress toward reinnervation than have the deeper, dermal fibers. Little if any attempt at reinnervation is seen on the ventral surface. In some preparations one finds a completely denervated zone which may reach a diameter of 12 millimeters. A 1 millimeter fringe of partial innervation surrounds the denervated area. Pinprick sensation is absent in the hypertrophic scar, but is present beyond this.

Three weeks. There is little change in the gross appearance of the burns between the second and third weeks, but the area contracts somewhat so that the gross estimate of damage is about 10 millimeters. A few hairs appear in the area surrounding the central slough. Superficial, beaded fibers occasionally appear in the zone of hypertrophic scar formation, and a rare fiber is seen as much as 1 millimeter central to the nearest surviving hair follicle. The most peripheral area of the burn now has a good nerve supply. The area of absence of innervation is only 5 to 7 millimeters in diameter, with scanty innervation 1 millimeter beyond this, and obviously thinned innervation for a further 1 millimeter. Regeneration of nerve fibers on the ventral surface is still behind that on the dorsal surface. There is no nocifensive response to pinprick in the area of hypertrophic scar.

FIG. 11. Small, deep dermal nerve trunks persisting in a burned area 1 hour after exposure. ×73.
FIG. 12. Hyperemia and absence of nerve fibers in burned area 18 hours after exposure. ×73.
FIG. 13. Absence of nerve fibers in burned area 48 hours after exposure. Ventral surface. ×73.

Four weeks. There is no marked change from the gross appearance at 2 and 3 weeks. Reinnervation has progressed to the point at which many nerve fibers are present in the area devoid of hair follicles. Nerve trunks of only 2 and 3 fibers are common, but single fibers are still prominent if not the rule. Myelinated and nonmyelinated nerve fibers are again found in the same trunk, and beaded terminals can be traced back to small, myelinated nerve fibers. Hair follicle reinnervation seems to consist wholly of beaded fibers. Reinnervation of the ventral surface has progressed remarkably and is just about equal to that on the dorsal surface. Pinpricks are now felt in the area of hypertrophic scar.

Seven weeks. The central hole is present, and immediately surrounding this there is no hair. However, there is more hair in the peripheral zone of hypertrophic scarring than there was at 4 weeks. Where hair follicles are numerous, innervation appears to be nearly normal. Centrally, where no hair follicles are found, reinnervation has progressed and many small nerve trunks are seen. The most prominent defect is a decrease in the number of fibers per trunk rather than a decrease in the number of trunks. The nerve fiber patterns on the ventral surface are almost normal up to the sloughed area.

DISCUSSION

The distinction between second and third degree burns is sometimes difficult and is always important. Aids in making the correct evaluation include biopsy, in situ staining, intravenous fluorescein, and sensory testing. Jackson reviewed the limitations of these methods and presented a brief review of the literature on sensory changes in cutaneous burns. His own work points to the superiority of sensory testing over the other methods since biopsy is not practical except in limited areas and the other techniques are not reliable.

It is shown that a radiant energy burn of moderate intensity and short duration destroys some nerve fibers almost immediately. The central area of the burn is devoid of nerve fibers, and pinpricks produce no response. However, nerve fibers which appear normal and which conduct sensation as late as 4 hours after burning will degenerate at a later time. Most of the neural damage is evident by 18 to 24 hours after injury, but some degeneration takes place as late as the second and third days following the burn.

In evaluating the depth of a burn on the basis of response to pinprick it should be borne in mind that this sensation may be lost in certain specialized areas (palms, soles of feet, face, and scalp) which will heal satisfactorily without grafting. If the observations presented are applicable to other types of burns and to human skin, they suggest that another consideration, the time between injury and testing, is of some importance. The area in which sensation and nerve fibers are absent 4 hours after injury

sloughs centrally and heals peripherally with the formation of thick scar tissue and scar epithelium. In addition, there is a further peripheral zone in which sensation and nerve fibers are initially present, although the nerve fibers may show some decrease in number, which will also heal by scarring. The area in which nerve fibers and pinprick sensation are absent at 24 hours roughly corresponds to the area which heals chiefly by scar formation. An exact correlation cannot be made because the wound contracts a little as it heals, and it is impossible to determine the innervation and then observe the healing of any one area. The areas in which nerve fibers and pinprick sensation are present at 24 hours heal rapidly by epithelialization from hair follicles.

Reinnervation of the injured area begins early but proceeds slowly. As early as the fourth postburn day isolated, new branches are found, but even at the end of 2 weeks little progress has been made. Reinnervation during this time takes the form of single fibers rather than small nerve trunks. The peripheral zone is well innervated in 3 weeks, but the central area remains scantily supplied. A nearly normal nerve fiber pattern is found at some time between 4 and 7 weeks after the injury. Up to that time normal, multiple innervation of a given area is not seen, the isolated fiber or single innervation being the rule. A similarly altered pattern of innervation could account for both hypesthesia and changes in the quality of pain sensation in the injured area in humans (3).

It should be noted that dense scar tissue adjacent to a less severely damaged area will contain many nerve fibers in 4 weeks. It would, of course, be unwise to base any conclusion on damage or type of healing on sensory performance at this late time. However, to my knowledge, no such suggestion has ever been made.

The observations on the ventral skin of the ear have little bearing upon clinical problems. This tissue has, so to speak, been burned from the inside out since the deeper layers are subjected to more energy than are the superficial layers. One may thus observe reinnervation of relatively normal superficial dermis and epithelium by branches of deep nerve fibers recovering from injury. It is only worth mentioning that there is a relatively long latent period, but that reinnervation, once begun, proceeds rapidly.

SUMMARY AND CONCLUSIONS

1. Degeneration and regeneration of nerve fibers have been investigated in areas of rabbit skin which have been injured by radiant heat.

2. Neural degeneration is only partly developed 4 hours after injury, is nearly complete in 24 hours, but is somewhat progressive during the first 4 days.

3. The possible relationships of these findings to sensory testing of a burned area are discussed.

4. A relationship between sensory and neural loss and the manner of healing is pointed out.

5. Reinnervation of the injured area proceeds slowly and is still not quite normal at the end of 7 weeks.

6. The neural patterns seen during reinnervation are mentioned briefly and are related to altered qualities of sensation in a healing area.

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THE UPTAKE OF RADIOSULFUR IN THE FRACTURED HUMERUS IN THE RAT

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IT HAS PREVIOUSLY BEEN SHOWN by Dziewiatkowski (1, 2) that radiosulfur (S^{35}) injected into the rat as sodium sulfate is readily demonstrable in the long bones of the skeleton within a few hours of injection. The radiosulfur shows a particular predilection for the cartilage associated with these bones in their epiphyses and articular surfaces, apparently being incorporated into the cartilage in organic form as chondroitin sulfuric acid.

It is also well known that a definite cartilaginous phase is present during the normal process of fracture repair in long bones, the cartilage being laid down in varying amounts at the fracture site and then transformed into bone by the process of endochondral ossification. The amount of cartilage which may be laid down in any given fracture is quite variable, and the factors controlling its deposition are not well understood. Watson-Jones believes, however, that lack of immobilization of the fragments will tend to cause an increase in the amount of cartilage appearing during repair. Should this be true, one might expect a greater uptake of radiosulfur by unsplinted than by splinted fractures.

The purpose of our present study was, firstly, to compare the uptake of radiosulfur of the fractured rat humerus with that of the symmetrically opposite intact bone and, secondly, to compare the relative uptakes of splinted and unsplinted fractures.

MATERIALS AND METHODS

Adult female rats of the Wistar strain, varying in weight from 180 to 280 grams and fed ad libitum with commercial Purina dog chow were used in the present experiment.

Under ether anesthesia, a closed complete fracture of 1 humerus was produced in each of a series of 40 rats by grasping the foreleg between fingers and thumb of each hand and snapping the bone at its midportion. The animals were then returned to their cages and all made a satisfactory recovery, limping about and eating normally within a few hours of recovery from anesthesia. Three weeks following the fracture 20 of the rats were sacrificed; at 6 weeks, 10 more; and at 8 weeks the remaining 10.

A further series of 12 rats was prepared in similar fashion, except that a gypsona plaster bandage was applied in the form of a shoulder spica with the traumatized limb bound to the trunk to immobilize the fracture as far as possible. The plasters remained in place satisfactorily in all cases, but 2 of the rats died within a week of their application. The remaining 10 rats were sacrificed 3 weeks following the fracture.

All animals received 200 microcuries of radiosulfur by intraperitoneal injection 24 hours prior to sacrifice. The dose was dissolved in 2 milliliters of distilled water together with 8 milligrams of sodium sulfate.

Measurement of radiosulfur. Following sacrifice, the normal and fractured humeri were carefully and cleanly removed from each animal and dried at room temperature for 24 hours, following which their weights were recorded. The bones were then dissolved by a nitric-perchloric acid wet-digestion technique designed to oxidize all organic sulfur present to an inorganic form prior to its precipitation as barium sulfate.

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This constituted a modification of the method originally used by Gieseking and associates for the ashing of organic plant material. In this technique two oxidizing solutions were used, the compositions of which were as follows:

Solution A:	Concentrated nitric acid	—3 parts
	Distilled water	—1 part
Solution B:	Perchloric acid 72 per cent	—5 parts
	Concentrated nitric acid	—2 parts
	Distilled water	—3 parts

Approximately 7 milliliters of solution A were added to each gram of tissue in pyrex Erlenmeyer flasks and gentle boiling carried out in the fume cupboard until the contents of the flasks were reduced by one-half. Then, after cooling, 5 to 10 milliliters of solution B were added to each sample and gentle boiling carried out as before until a clear solution resulted. The mixture was again cooled, diluted one-half with distilled water, and heated to dryness in the fume cupboard. After cooling, 5 milliliters of concentrated hydrochloric acid were added to each flask and the contents again taken to dryness. The resultant residue was dissolved in 15 milliliters of 1 normal hydrochloric acid, transferred to a beaker, and 50 milliliters of 0.3 per cent sodium sulfate added to provide carrier sulfate. Distilled water was added to 300 milliliters, the resultant solution heated to 90 degrees C., and the contained sulfur then precipitated as barium sulfate by the addition of 50 milliliters of 2 per cent barium chloride.

After standing overnight the resultant precipitate was transferred to centrifuge tubes, washed twice with distilled water and with absolute alcohol, and then transferred to planchettes for counting. Counting was carried out using a thin mica window Tracerlab G-M tube and a Tracerlab superscaler S.C. 18 for recording. The results were expressed in counts per minute (c.p.m.) per milligram of tissue.

Radioautographs. Radioautographs were prepared by provoking fracture of 1 humerus in a further series of 6 rats, injecting the usual dose of 200 microcuries of S^{35} 3 weeks following the fracture, and then sacrificing the animals 24 hours later. The fractured and intact humeri were removed, dried, and then worn down to a thin flat shape by friction with emery paper. The prepared bones were then placed against sheets of super XX photographic film in a darkroom and, after suitable wrapping, left in contact with the film for 2 weeks. At the end of that time the film was developed in routine fashion to produce the radioautograph.

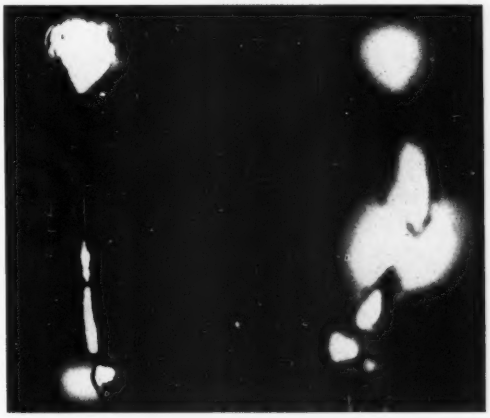

FIG. 1. Radioautographs to demonstrate the uptake of radiosulfur by fractured rat humeri 3 weeks following fracture. (Fractures were unsplinted.)

RESULTS

The results are summarized in the accompanying tables. Table I illustrates the findings at various time intervals after frac-

TABLE I.—RADIOSULFUR IN INTACT (I) AND FRACTURED (F) HUMERI OF RATS AND F/I RATIO AT VARIOUS TIME INTERVALS AFTER FRACTURE

Time after fracture, wks.	*No. of rats*	*Values*	*Intact humerus c.p.m./mgm.*	*Fractured humerus, c.p.m./mgm.*	*F/I ratio*
		Mean	3.7	7.9	2.2
3	20	S.D.	1.5	2.1	0.4
		Range	2.1—6.9	5.4—12.2	1.5—2.9
		Mean	2.4	3.2	1.3
6	10	S.D.	1.0	1.7	0.5
		Range	0.8—3.9	1.3— 6.4	0.7—2.3
		Mean	1.9	2.3	1.2
8	10	S.D.	0.3	0.4	0 1
		Range	1.3—2.5	1.7— 3.0	1.0—1.4

S.D., standard deviation.
c.p.m./mgm., counts per minute per milligram of tissue.

TABLE II.—EFFECT OF SPLINTING ON UPTAKE OF RADIOSULFUR BY FRACTURED HUMERUS EXPRESSED AS F/I RATIOS

Condition of fracture	*No. of rats*	*F/I ratio*	
Unsplinted	20	Mean	2.2
		S.D.	0.4
		Range	1.5—2.9
Splinted	10	Mean	1.6
		S.D.	0.2
		Range	1.1—1.8

S.D., standard deviation.

ture. The results are best interpreted by reference to the F/I ratios listed in the extreme right hand column. This figure refers to the ratio of the uptake of S^{35} by the fractured humerus as compared to the corresponding intact bone, both values having been expressed as counts per minute per milligram of tissue. It will be seen that at 3 weeks after fracture the uptake by the fractured bone was on the average 2.2 times as great as that of the intact bone. At this stage clinical union of the fracture had not yet occurred, the fractured ends being loosely bound together by primary callus. At 6 weeks, 2 of the 10 fractures showed clinical union and the other 8 a quite firm fibrous union, and at 8 weeks all but 2 of the fractures exhibited clinical union. This progressive healing of the fractures was marked by an accompanying drop in the uptake of S^{35}, the F/I ratio falling to values of 1.3 and 1.2 respectively.

Table II shows that the marked elevation of F/I ratio (2.2) occurring in the 3 week old unsplinted fractures could be reduced to 1.6 simply by applying a plaster cast to the injured extremity. This would tend to support the contention that movement at the fracture site encourages cartilage formation, although histologic studies to confirm this point were not done.

Representative radioautographs are pictured in Figure 1. The general pattern of uptake in the normal bones is similar to that described by Dziewiatkowski and others. The fractured bones show a heavy deposition of radioactive material in the region of the fracture site, suggesting that a large part of the increased uptake occurs in the immediate vicinity of the fracture.

SUMMARY

1. A method for the study of the uptake of radioactive sulfur in the bones of rats is described.

2. The use of this method discloses that the fractured humerus shows an increased uptake of S^{35} at 3 weeks following the fracture, this increase then diminishing as fracture healing proceeds further.

3. The increase in uptake by the fractured bone is lessened by splinting the fracture.

4. This method offers a useful experimental means for the investigation of the course of fracture healing.

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CARCINOMA OF THE COLON AND RECTUM ASSOCIATED WITH CHRONIC ULCERATIVE COLITIS

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CARCINOMA OF THE COLON or rectum associated with chronic ulcerative colitis is rarely encountered in a general hospital. However, in hospitals and clinics treating many cases of colitis recognition of this serious complication is being made with increasing frequency. Interest in this complication of colitis was aroused by Bargen's report (2) of 17 cases of carcinoma in 1928, and since then his associates at the Mayo Clinic and many other surgeons and pathologists have discussed the characteristics of this disease.

This article is an analysis of 12 cases of carcinoma of the colon and rectum found during the course of 182 consecutive colectomies for ulcerative colitis performed at St. Mark's Hospital between 1949 and 1955 inclusive. The incidence of malignancy in this series of surgically treated patients was therefore 6.6 per cent. Other cases of carcinoma complicating ulcerative colitis were encountered at St. Mark's Hospital during this same period but have not been included since they were not among the cases of colectomy but were found at postmortem examination or at laparotomy. The first 3 cases in this present series have been previously reported by Counsell and Dukes.

REVIEW OF LITERATURE

Before describing the cases from the records of St. Mark's Hospital reference should be made to the experiences of others.

In 1927 Yeomans reported a case of carcinoma associated with ulcerative colitis but the first large series was published by Bargen (2) who described 17 cases from the Mayo Clinic. A few years later Bargen and Dixon (3) reported another 7 cases, and Bargen and Sauer (4) presented an additional 30 cases from 1935 to 1944. In 1949, Sauer and Bargen added still another 41 cases to the total reported from the Mayo Clinic. Awareness of the association of cancer with colitis has certainly increased over the past 10 years as indicated by the steadily increasing number of articles reporting carcinoma complicating ulcerative colitis.

The actual incidence of cancer following ulcerative colitis has varied very greatly in reported cases, which is not surprising since some of the calculations have been based upon patients treated surgically, others upon medical cases, and others upon casual postmortem findings. The figures have ranged between 1 and 11 per cent.

A number of writers have published reports of cases of carcinoma associated with medically treated series of ulcerative colitis and they give the following incidences. Streickner found an incidence of 1.4 per cent in a series of 217 cases of ulcerative colitis. Rickets and Palmer described 3 cases of cancer among 206 patients, an incidence of 1.4 per cent. Cattell and Boehme (7) reported 450 cases with an incidence of 2 per cent. Johnson and Orr gave an incidence of 3.2 per cent in a series of 164 cases. Kasick, Weingarten, and Brown, reporting a series of 143 consecutive cases of severe ulcerative colitis, gave an incidence of cancer of 4.9 per cent. In 290 cases reported by Svartz and Ernberg (30), 9 were found to be carcinomas, an incidence of 3.1 per cent. Glecker and Brown described 12 cases from a series of 316 cases, giving an incidence of 3.8 per cent. In a series of 129 cases of ulcerative colitis in which 4 patients were found to have carcinoma, Rice-Oxley and Truelove gave an incidence of 3.1 per cent. Svartz

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(29) found an incidence of 3.1 per cent of 290 cases, and Weckesser and Chinn reported 118 cases in which 4 were found to have cancer, an incidence of 3.4 per cent.

There have been a few large series of cases of ulcerative colitis published, and their incidence of carcinoma approximated that of the smaller series. Sloan, Bargen, and Gage (27) have followed 2,000 patients for an average of 9.7 years between the years of 1918 to 1938. Proved malignant disease was found in 65 cases, an incidence of 3.3 per cent. Jackman, Bargen, and Helmholtz found an incidence of 3.2 per cent in 871 cases. Lynn reviewed the literature up to 1945 and combined the number of cases in articles in which the incidence of cancer was reported in relation to ulcerative colitis. Twenty-eight cases of malignant disease in 1,467 cases of ulcerative colitis gave an incidence of 1.9 per cent. Thus, the average incidence of carcinoma complicating ulcerative colitis in medical series, excluding surgical or pathologic series, was found to be approximately 3 per cent.

In articles in which the material was surgical, the incidence was frequently much higher. Cattell (6) reported the incidence of cancer as 7 per cent of all cases of ulcerative colitis which came to surgery. Warren and Sommers described 120 surgical cases and 60 postmortem specimens and gave an incidence of 5 per cent. Counsell and Dukes gave an incidence of 11.1 per cent in a series of 63 colectomies for ulcerative colitis in which 7 patients were found to have carcinoma. Lyons and Garlock, however, found an incidence of only 3.9 per cent in 266 surgically treated patients.

A few authors have reported series of ulcerative colitis in which no carcinoma was found. The largest such series was published by Felsen and Walarsky. No malignancy was found in 855 patients, the majority of whom had been followed and examined for many years. Hardy, Brooke, and Hawkins stated that malignant disease was a rare finding in their experience. In a later publication, however, Brooke presented 2 cases of carcinoma complicating ulcerative colitis and was of the opinion that carcinoma was, in fact, a real danger in chronic ulcerative colitis. Cattell and Boehme (7) suggested that the low incidence of carcinoma in certain series was probably due to infrequent surgical intervention, and that in some cases death attributed to ulcerative colitis without postmortem examination might actually have been due to malignant disease.

CASE REPORTS AND PATHOLOGIC NOTES

The following histories and pathologic reports represent 12 cases of carcinoma associated with ulcerative colitis found in a series of 182 consecutive colectomies for ulcerative colitis at St. Mark's Hospital. The majority of these cases were suspected or diagnosed as malignant before operation.

CASE 1. S. S., a 54 year old married female, on first admission gave a history of at least 8 years' diarrhea and bleeding per rectum. She was anemic and blood transfusion was necessary. Seven months later a hard mobile mass was found in the middle third of the rectum, and she was admitted to the hospital. Biopsy revealed anaplastic adenocarcinoma. An ileostomy was performed by Mr. C. Naunton Morgan, and 6 weeks later a palliative synchronous combined excision of the rectum was carried out. Secondary liver and peritoneal deposits were found at operation. She died suddenly 3 weeks after operation. No postmortem examination was done.

Operation specimen showed a protuberant growth in the rectal ampulla. Sections revealed anaplastic spheroidal cell carcinoma simplex which had spread into perirectal tissues and given rise to peritoneal plaques and 4 involved lymph nodes. The surrounding mucous membrane was very atrophic and replaced in part by granulation tissue.

CASE 2. E. S., a 47 year old male, when first seen gave a history of recurring attacks of diarrhea for more than 24 years. The rectal mucosa was granular and showed an early stricture. He returned for further treatment 13 years later at the age of 60, and a dense rectal stricture was found which prevented digital or instrumental examination. An inoperable fistula was present. A terminal ileostomy was carried out by Mr. W. B. Gabriel followed 3 weeks later by a right hemicolectomy. The patient's general health improved and 9 months later the remainder of the colon was resected. The rectum was removed by perineo-abdominal excision after another 6 months. There was no sign of recurrence 5 years later.

Examination of the second operation specimen revealed an unsuspected carcinoma in the descending

colon. A 6 inch stricture occupied the splenic flexure. Sections showed adenocarcinoma of low grade malignancy which had spread locally. There were no lymphatic metastases.

CASE 3. A. J., a 54 year old female, when first seen complained of feeling an obstruction in the rectum. She had had periodic attacks of diarrhea for 3 years. Rectal examination revealed a large soft villous tumor in the lower third of the rectum and a protuberant carcinoma immediately above. Synchronous combined excision of the rectum was carried out by Mr. H. R. Thompson. Recovery from operation was slow. Profuse discharge from the colostomy necessitated a terminal ileostomy 3 months after operation, and this was followed after an interval of another 3 months by subtotal colectomy. The wound broke down and the patient died from peritonitis 3 weeks following operation.

Examination of the rectal specimen showed a colloid carcinoma arising in a pre-existing villous papilloma and associated with ulcerative colitis. The growth had spread locally, and 1 lymphatic metastasis was present.

CASE 4. A. G., a 57 year old male, was admitted with a history of colitis for 16 years. Two months prior to admission he experienced an attack of severe abdominal pain. Barium enema showed a carcinoma of the splenic flexure. An ileostomy and subtotal colectomy were carried out by Mr. C. Naunton Morgan. Four months later a synchronous combined excision of the rectum was performed. There was no sign of recurrence 3 years later.

Examination of the first operation specimen revealed 4 constricting growths situated in the: (a) cecum, near the ileocecal valve, (b) transverse colon, (c) splenic flexure, and (d) descending colon. The constriction in the descending colon proved to be an inflammatory stricture with hyperplastic changes in the submucosa, but at its margin an adenomatous tumor was found in which there was a small focus of carcinoma in the preinvasive phase. The other 3 tumors were constricting carcinomas of average grade of malignancy and had spread locally. There were no lymphatic metastases. A number of inflammatory polyps were scattered throughout the colon and were sectioned. The rectum showed evidence of ulcerative colitis.

CASE 5. W. F., a 37 year old male, when first seen gave a history of 5 years' diarrhea, passing blood and pus per rectum. X-ray examination showed involvement of the whole colon. He was followed as an outpatient for 8 years during which time he had periodic attacks of diarrhea and bleeding. At the age of 45, he finally gave consent for operation, and an ileostomy and total colectomy were performed by Mr. H. R. Thompson. He regained health very rapidly and is alive and well 3 years later.

Examination of the operation specimen revealed widespread involvement of the colon. Several large polypoid granulomatous tumors were present in the cecum and the ascending and descending colon, and there was an inflammatory stricture at the splenic flexure. Microscopic examination revealed marked inflammatory reaction in the mucosa. Polyps were characterized by a very fibrous and vascular stroma. Mucosal repair was noted in many places. One of the tumors of the transverse colon contained a number of cysts filled with mucus. One cyst contained a small focus of low grade, early colloid carcinoma with commencing invasion of submucosa. No lymph glands were involved.

CASE 6. O. D., a 36 year old married female, when first seen gave a history of attacks of diarrhea since the age of 19. An appendicostomy had been performed at 23 years. Sigmoidoscopy revealed 3 polyps in the rectum, and biopsies showed the tumors to be adenomas containing areas of malignancy still in the preinvasive phase. Ileostomy, total colectomy, and synchronous combined excision of the rectum were performed by Mr. J. C. Goligher in one stage. The postoperative period was uneventful. There was no sign of recurrence 4 years later.

Mucosa of the operation specimen was pale and atrophic without obvious ulceration, but sections showed mucosal atrophy and fibrosis. Five additional carcinomas were discovered. A little local thickening in the mucosa of the transverse colon showed an early stage colloid carcinoma. In the rectosigmoid, a small nodule with a small ulcer on its surface revealed a focus of anaplastic carcinoma with local spread. Another small focus was found nearby. In the upper third of the rectum, a semiulcerated nodule contained an early stage carcinoma. Another microscopic focus was found nearby in a chance section. A number of adenomatous polyps sectioned were not malignant. Eight carcinomas were found in this case. There were no lymphatic metastases.

CASE 7. M. C., a 73 year old married female, was first admitted with a history of attacks of diarrhea for 15 years. For a year she had complained of transient abdominal pains, and a change in bowel habit had been noticed over the past 6 months with a trace of blood per rectum. X-ray examination revealed carcinoma of the sigmoid colon. A left hemicolectomy and restoration of continuity was performed by Mr. E. T. C. Milligan. Multiple deposits were noted in the liver. The patient died 1 year later.

Operation specimen showed an annular carcinoma of the sigmoid colon of low grade malignancy with extensive local spread and lymphatic metastases. Mucosa below and 4 inches above the growth was normal. From this point the mucosa became gradually granular with a few scattered ulcers. More proximal still the bowel was contracted, and there were areas of complete mucosal destruction. At the proximal end of the specimen the ulceration was restricted to longitudinal strips which corresponded exactly with the longitudinal muscle coat.

TABLE I.—SUMMARY OF FINDINGS

Case No., Sex, Age at onset of ulcer. col., yrs.	*Duration of ulcer. col. before finding ca., yrs.*	*How ca. diagnosed*	*Site of ca.*	*No. of ca.*	*Histology and grading*	*Stage*	*Outcome*
1 F 55	8	Clinically (biopsy)	Rectum	1	Carcinoma simplex, high grade	C Liver and peritoneal deposits	Death, 1 mo.
2 M 61	37	Unexpected (pathologist)	Descending colon	1	Adenocarcinoma, low grade	B	Alive and well, 5½ yrs.
3 F 54	3	Clinically (biopsy)	Rectum	1	Colloid carcinoma, average grade	C	Death 3 wks., peritonitis
4 M 57	16	Radiologically	Multiple	4	Adenocarcinoma, average grade	B	Alive and well, 3 yrs.
5 M 45	13	Unexpected (pathologist)	Transverse colon	1	Colloid carcinoma, low grade	A	Alive and well, over 3 yrs.
6 F 36	18	Clinically (biopsy)	Multiple	8	Colloid (and 1 anaplastic), early (and high)	A, B	Alive and well, 4 yrs.
7 F 73	15	Radiologically	Sigmoid colon	1	Adenocarcinoma, low grade	C Liver and peritoneal deposits	Death, 1 yr.
8 F 56	10	Unexpected (pathologist)	Splenic flexure	1	Colloid carcinoma, low grade	B	Alive and well, 1½ yrs.
9 F 33	16	Clinically and radiologically	Splenic flexure	1	Colloid carcinoma, high grade	C Peritoneal deposits	Death, 3 mos.
10 M 55	20	Unexpected (laparotomy)	Sigmoid colon	1	Adenocarcinoma, low grade	B	Alive and well, 1 yr.
11 F 52	38	Clinically (biopsy)	Rectum	1	Squamous cell carcinoma, low grade	B	Alive and well, 9 mos.
12 F 30	9	Clinically (biopsy and laparotomy)	Rectum and transverse colon	2	Anaplastic, high grade	B, C	Alive and well, 2 mos.

Stage I or A case: growth limited to rectum or colon.
Stage II or B case: growth extending beyond bowel but no lymphatic metastases.
Stage III or C case: lymphatic metastases present.

CASE 8. R. T., a 56 year old married female, when first seen complained of abdominal pain each time she passed blood-stained mucus per rectum. She gave a history of 10 years of ill health due to diarrhea. An ileostomy had been performed 8 years previously with some improvement after 3 years in the hospital. Arthritis of both knees had developed. Barium enema showed complete obstruction of the colon. A subtotal colectomy with refashioning of the ileostomy was performed by Mr. C. Naunton Morgan, and a synchronous combined excision of the rectum was carried out 4 months later. She is alive and well a year and a half later.

First operation specimen showed the colon to be grossly contracted and surrounded by a fibrofatty envelope and its lumen barely admitted a probe. A hard stricture was present above the cecum, and at the splenic flexure a second stricture existed due to colloid carcinoma of low grade with local spread. There were no lymphatic metastases. The rectum was contracted and fibrosed.

CASE 9. V. S., a 33 year old married female, on admission gave a history of 16 years' diarrhea. A large mass was palpable below the left costal margin, and the patient had a low grade fever. Carcinoma was diagnosed clinically and on x-ray examination, which also showed colitis affecting the whole colon. Resection of splenic flexure, spleen, and descending colon with restoration of continuity was carried out by Mr. O. V. Lloyd-Davies. The patient died 3 months after operation.

Operation specimen showed a constricting tumor 13 inches in length. The lower pole of the spleen was firmly adherent. Microscopic examination revealed colloid carcinoma of a high grade of malignancy containing many signet ring cells. There was extensive

local spread and many of the regional lymph glands contained metastases.

CASE 10. M. P., a 55 year old male, was admitted to the hospital as an emergency patient with intestinal obstruction. He gave a history of colitis for 20 years. Laparotomy by Mr. H. E. Lockhart-Mummery revealed carcinoma of the lower descending colon and a cecostomy was done. Two and a half weeks later a subtotal colectomy and ileorectal anastomosis were performed. The terminal 10 inches of ileum appeared to be the site of Crohn's disease and this was resected. Postoperative recovery progressed satisfactorily.

Operation specimen showed a constricted terminal ileum with a granular mucosa and ulcerations throughout its length. This was thought to be Crohn's disease. The colon was shortened with a granular mucosa but the terminal 2 inches appeared normal. A 4 inch stricture occupied the lower descending colon and on section proved to be adenocarcinoma of a low grade of malignancy. At the margin of the growth there was an area in which the appearance was very anaplastic and invasive in nature. There was extensive local spread but no lymphatic metastases.

CASE 11. M. H., a 52 year old female, was admitted to the hospital with a history of attacks of diarrhea with blood and mucus for 38 years. Rectal pain and marked bleeding per rectum had been present for 1 month. Examination under anesthesia was done. A hard indurated mass was felt in the left of the pelvis, and an irregular ulcer on the posterior rectal wall was biopsied and showed squamous cell carcinoma on section. A rectovaginal fistula was noted. An ileostomy, total colectomy, and synchronous combined excision of the rectum were performed by Mr. O. V. Lloyd-Davies. There was no recurrence 6 months later.

Operation specimen showed a normal colon from cecum to splenic flexure. The lower descending colon, sigmoid, and rectum were shortened and contracted with a very narrow lumen. The ulcerating tumor in the lower third of the rectum showed a well differentiated squamous cell carcinoma of a relatively low grade of malignancy on section. There was local spread but no glands were found in the mesorectum. The mucosa of the lower rectum had been replaced by an extensive area of leucoplakia which surrounded the carcinoma.

CASE 12. J. P., a 30 year old married female, on admission gave a history of attacks of diarrhea for 9 years. She had been fairly well for 2½ years but over the past 6 months she complained of marked loss of weight and diarrhea with blood and mucus. Sigmoidoscopy showed a relatively quiescent mucosa but at 7 centimeters a large sessile growth was discovered. Biopsy showed anaplastic carcinoma. Barium enema indicated widespread colitis. Proctocolectomy and ileostomy were carried out in one stage by Mr. O. V. Lloyd-Davies.

The mucosa of the operation specimen was of the healing phase. The midpoint of the transverse colon was occupied by a large annular carcinoma which was missed at x-ray examination because it hung down into the pelvis. Sections revealed both the colon and rectal tumors to be anaplastic carcinoma and contained a remarkable number of mitotic figures. The rectal tumor showed submucosal but no muscular spread and 1 of 25 glands contained secondary deposits. The tumor of the colon had spread into the bowel muscles. There were no metastases in the 30 glands examined.

DISCUSSION

In this series of cases of carcinoma associated with ulcerative colitis reported from St. Mark's Hospital, there were a number of observations which confirmed certain points made by Counsell and Dukes. But on other aspects there was a variance. These 2 series, however, were not quite comparable because of the difference in available material. Six of their cases were from other hospitals (surgical and postmortem). In this series, all the cases were from St. Mark's Hospital and were found in 182 consecutive colectomy specimens undertaken for ulcerative colitis. Inoperable carcinomas and malignant lesions found at postmortem examination were not included.

Many writers have observed and recorded the fact that carcinoma is likely to develop in patients with ulcerative colitis of 10 to 15 years' or more duration. In this series of patients with malignant disease, the average duration of ulcerative colitis was found to be 17 years. In 182 cases, there were 46 patients with ulcerative colitis which had lasted for over 10 years and in 9 of these carcinoma developed. Of the 136 patients who were affected by the disease for less than 10 years, there were only 3 cases of malignant disease. Shands, Dockerty, and Bargen observed that in 73 patients with carcinoma 65 per cent had symptoms of ulcerative colitis for 10 years or more.

The average age at the time of diagnosis of carcinoma was 50 years; the oldest patient was 73 and the youngest 30 years old. This average age was 10 to 15 years earlier than that found in the general population

affected by carcinoma. Others have placed this average at an even earlier age. Shands, Dockerty, and Bargen gave an average age of 42 years in 73 patients with carcinoma. Sloan, Bargen, and Baggenstoss (26) reported a mean age of 42 years and they observed that 80 to 90 per cent were over 40 years old. Warren and Sommers gave an average age of 41 years and Weckesser and Chinn's patients were all 35 years old or younger. Ascherman reported a very early average of 32 years.

Some authors have noted that the age of onset of ulcerative colitis was significant. Jackman and associates stated that the incidence of malignancy was almost twice as high if the disease began before 16 years, and Cattell and Boehme (7) observed that the incidence of carcinoma was high if children were affected by ulcerative colitis. In this series only 1 patient developed symptoms before 16 years of age and none of Counsell's or Dukes' patients were affected before this age.

The ratio between male and female in ulcerative colitis is of some interest. Warren and Sommers stated that the sex distribution in this disease was equal or perhaps a slight preponderance of females. The ratio in this series of 182 patients was equal. However, in the patients affected by carcinoma the distribution was 4 males to 8 females. Counsell and Dukes' figures were 3 males and 10 females. In a large series of cases of carcinoma associated with ulcerative colitis Sauer and Bargen reported a ratio of 20 males to 21 females. According to the Registrar General, males are affected more by carcinoma of the rectum and colon than females in the general population, and Ascherman analyzed 461 patients coming to postmortem without ulcerative colitis and found that the ratio was 65 per cent males to 35 per cent females. It is probably not wise to judge, as yet, whether there is an actual increase in the ratio of females over males affected by carcinoma associated with ulcerative colitis.

There were 23 carcinomas discovered in the 12 patients and the site of these growths has been plotted (Fig. 1). It was noted that their distribution approximated that found in subjects with carcinoma but not affected by ulcerative colitis. Three of the patients had multiple malignant lesions. In Case 6, 8 carcinomas were discovered associated with adenomatous polyps and in Case 4, 4 carcinomas were found. Sloan, Bargen, and Gage (27) reported 12 cases of multiple carcinomas of 85 cases of carcinoma.

Some authors have found that carcinoma associated with ulcerative colitis was usually of a high grade of malignancy associated with early lymphatic spread and a rapidly fatal outcome. This observation was not made in this series. Of the 23 tumors found, 18 were histologically graded as of average or low grade malignancy, and in 7 of these cases no lymphatic spread was found. Dukes has observed that in other cases of carcinoma of the rectum and colon approximately half showed no lymphatic spread. Crile believed that the malignancy which developed in ulcerative colitis was almost invariably incurable and that even a small carcinoma had a poor prognosis. Others have also expressed this view. However, 8 of the 12 patients in this article were still alive and well at the time of writing. One patient (Case 2) was still alive and well 6 years later and another patient (Case 6) was also alive 4 years after operation. Two patients (Cases 4 and 5) had survived well over 3 years since surgery and the patient in Case 8 was well a year and a half later. One patient reported by Counsell and Dukes was alive with no signs of recurrence after her operation in 1947. The reasons for the better prognosis of the patients in this series were probably twofold: (1) that in recent years surgery of acute and chronic ulcerative colitis has been undertaken at an earlier stage before carcinoma had a chance to develop or, if present, to disseminate and (2) that the probability of carcinoma complicating these cases had been anticipated. Eight of the 12 cases discussed in this article were diagnosed as malignant before operation clinically, radiologically, or by positive biopsy.

The gross characteristics of the majority of carcinomas in this group closely paralleled the types of malignant growths found in the colons and rectums not affected by ulcerative colitis. Of these, a high proportion were of the annular or constricting type. As inflammatory strictures or marked spasm are common and accepted findings in x-ray and sigmoidoscopic examinations of cases of ulcerative colitis it would be reasonable to regard these areas with some suspicion in the long standing cases. A carcinoma could easily be mistaken for an inflammatory stricture and it is frequently difficult to distinguish the two. Close supervision, clinically and roentgenologically, is necessary, and marked changes in bowel habit, bleeding, or loss of weight, particularly in the quiescent stage, should suggest that the possibility of malignancy is very real. Occasionally, malignant disease may present an atypical appearance. A diffuse submucosal spread over wide areas has been observed by Shands, Dockerty, and Bargen. In this group, Case 11 presented a stricture of the rectum with a squamous cell carcinoma superimposed on leucoplakia.

Multiple carcinomas are frequently found in cases of malignant tumor associated with chronic ulcerative colitis. These tumors may present as separate and distinct primary growths in different parts of the colon and rectum, and they may or may not be of the same histologic grading. Cases 4 and 12 illustrated these points. Shands, Dockerty, and Bargen suggested the removal of any other part of the colon with ulcerative colitis if carcinoma was found because of this high incidence of multicentric growth. Multiple carcinomas may also present as malignant changes in a colon affected by ulcerative colitis but which contained adenomatous polyps. Case 6 represented such a condition and contained 8 separate carcinomas arising in adenomatous polyps. The significance of these adenomatous polyps will be referred to later.

A great many writers have suggested that ulcerative colitis predisposes to carcinoma,

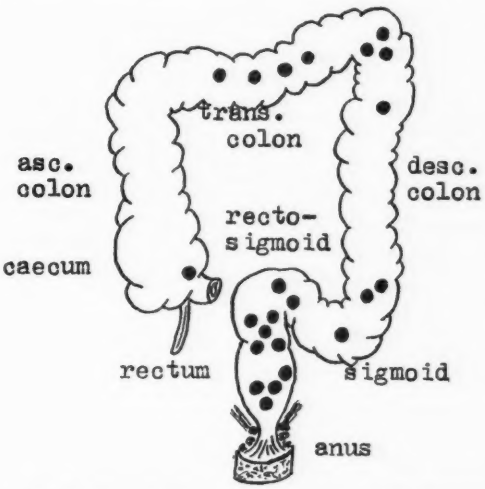

FIG. 1. Diagram showing the distribution of 23 primary tumors discovered in 12 cases of ulcerative colitis.

and certainly the incidence of malignancy is higher in these patients than in the general population and is higher in those patients suffering for more than 10 years. Carcinoma also manifests itself from 10 to 15 years or more earlier than cancer in the population as a whole. In addition, Dukes has observed that carcinoma tended to occur in chronic cases in the healing phase, and he noted that the mucosa was usually atrophic in appearance and on section. These observations were also encountered in this present series from St. Mark's Hospital (Figs. 2, 3, and 4). Shands, Dockerty, and Bargen also found that carcinoma developed in cases of healing or healed ulcerative colitis but was associated with a secondary mucosal hyperplasia. They did not see the flattened atrophic, "burnt out" appearance as reported by other authors. Dukes has suggested that, in ulcerative colitis, repair and destruction take place side by side and that from time to time fragments of mucosa become detached and buried in submucosa or even in the muscle coat. The commonest place to find misplaced tissue was at the margin of an abscess in the submucosa. This misplaced epithelium, he believed, might be a predisposing factor in the development of carcinoma.

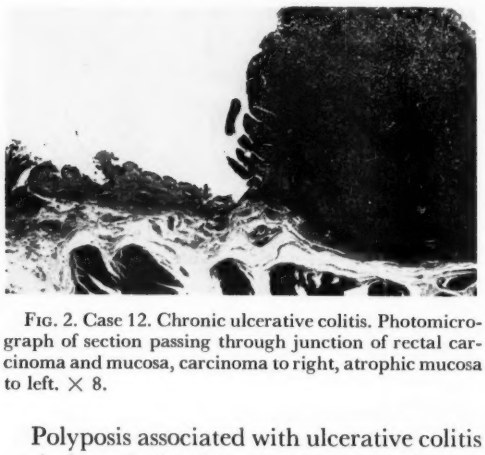

FIG. 2. Case 12. Chronic ulcerative colitis. Photomicrograph of section passing through junction of rectal carcinoma and mucosa, carcinoma to right, atrophic mucosa to left. × 8.

Polyposis associated with ulcerative colitis and the relationship to malignant disease has caused some difference of opinion and some confusion. Counsell and Dukes have done much to clarify these points in their article and have brought attention to the interpretation of these lesions. They observed that these polypoid projections occurred as 3 quite distinct varieties: (1) mucosal tags, (2) inflammatory polyps, and (3) adenomatous polyps. They did not think that the first 2 entities were in any way precancerous, and they noted that they might disappear spontaneously. Sloan, Bargen, and Baggenstoss (26) have also observed this fact. Warren and Sommers stated that no convincing case had yet been found in which inflammatory pseudopolyps had undergone malignant change. Felsen and Walarsky believed that when malignancy did develop in ulcerative colitis associated with pseudopolyposis that it probably did so as an entirely independent phenomenon, possibly arising from a pre-existing adenoma. In opposition to this view, Svartz (29), Crile, and Rankin believed that there was either a direct relationship between inflammatory polyposis and carcinoma or that it was a predisposing factor. Gabriel stated that polyposis should "constitute a grave warning of worse to come." Shands, Dockerty, and Bargen thought there was a possible relationship between the development of the inflammatory polyp and the pathogenesis of the malignant change. They observed in their series of cases that there was a "high incidence of pseudopolyposis in cases in which carcinoma was multicentric and a low incidence in the cases in which it was not multicentric." However, they noted that these inflammatory polyps were frequently seen in colectomy specimens in which no malignant change had occurred.

Adenomatous polyps are less common. They are true adenomas and are precancerous as are those found in colons not affected by ulcerative colitis. Warren and Sommers observed that adenomatous polyps were present in patients with ulcerative colitis to the same degree as the general population and with the same tendency to become ma-

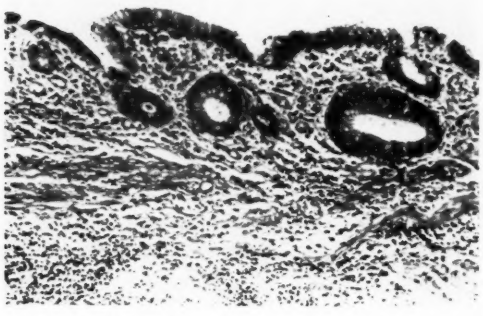

FIG. 3. Case 12. High power view of atrophic mucous membrane from Figure 2 as often seen in cases of long standing ulcerative colitis with carcinoma. × 80.

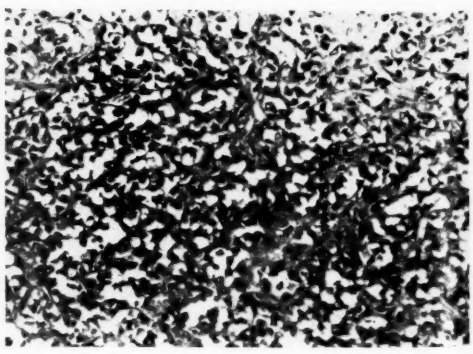

FIG. 4. Case 12. High power photomicrograph of anaplastic carcinoma of rectum from section shown in Figure 2. × 115

lignant, but they suggested that perhaps this tendency was accelerated by the inflammatory process of ulcerative colitis. Helwig considered that the presence of adenomatous polyps in colitis was coincidental and he believed that the incidence of adenomatous polyps increased with age, especially in the fourth decade. He stated that 1 in 5 persons who reached the age of 60 possessed an adenoma. It is suggested that, in cases of ulcerative colitis in which true adenomatous polyps have been discovered, closer supervision should be undertaken. The presence of these lesions might very well be added to the criteria to hasten the decision for radical surgery before the onset of malignant change.

CONCLUSIONS

Twelve cases of carcinoma of the colon and rectum found in 182 consecutive colectomies for acute and chronic ulcerative colitis have been reported. The following conclusions have been reached:

1. Carcinoma associated with ulcerative colitis occurred from 10 to 15 years earlier than in the general population.

2. The incidence of carcinoma in patients who had been affected by ulcerative colitis for 10 years or more was much higher than in patients of the same age and sex who have not had ulcerative colitis.

3. The policy of earlier colectomy for ulcerative colitis adopted in recent years has improved the prognosis of patients who develop malignant growths in the colon or rectum associated with ulcerative colitis.

4. "Stricture" areas in chronic cases of ulcerative colitis should be closely watched because strictures may prove to be the earliest evidence of malignant change. Some "strictures," however, are due to simple muscle spasm and others to inflammatory fibrosis.

5. Although it has often been reported that in carcinoma following ulcerative colitis the primary tumors were frequently atypical in appearance and distribution, in this particular series the characteristics of carcinoma associated with ulcerative colitis tended to take on the general pattern of ordinary carcinoma of the rectum and colon.

6. Malignant changes often first appeared in the quiescent stage of the disease when clinically the patient seemed to have improved.

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LYMPHATIC DISSEMINATION OF RADIOGOLD IN THE PRESENCE OF LYMPH NODE METASTASES

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THE TREATMENT OF LYMPHATIC METASTASES of malignant neoplasms by injection of radioactive colloids has been suggested by several investigators on the basis of the behavior of these colloids when introduced interstitially. When so injected they are disseminated by way of lymphatics until phagocytized primarily by reticuloendothelial cells in lymph nodes along afferent pathways. Relatively little of the radiocolloid reaches the systemic circulation to be deposited in reticuloendothelial cells elsewhere in the body. With sufficient dosage in both the experimental animal and in the human, it is possible to inflict severe radiation injury to lymphatics as well as lymph nodes. Several investigators have studied the feasibility of treatment of surgically inaccessible lymph nodes and have advocated the treatment of inoperable metastases of carcinoma of lung, cervix, and prostate by these methods. Realizing the inherent difficulties in evaluating the results of therapy on clinical grounds, certain pilot studies would seem indicated before continuing such treatment even on an experimental basis.

The eradication of cancerous lymph nodes by lymphatically disseminated radiocolloids would depend upon the ability of such lymph nodes to phagocytize sufficient quantities of the radiocolloid to result in their own destruction by radiation injury. This could occur in one of two ways: (1) with only partial replacement of a lymph node by cancer, continued function of the remaining lymphatic tissue should result in an effective phagocytic filter and subsequent damage to all tissues within effective radiation distance. Since the effective tissue penetration of the predominant ray (beta) from substances in common use is less than .5 millimeter, the mass of contiguous neoplasm must necessarily be small to be effectively treated; (2) if metastatic neoplastic tissue contained functioning lymph channels, it should be possible to effect radiation injury of the neoplasm regardless of whether or not a lymph node were completely replaced by cancer and regardless of the size of the mass.

Actually, little is known about the continued phagocytic function of a lymph node containing metastatic cancer, that is, whether significant lymph flow continues through uninvolved portions of the node or whether involvement of a lymph node by cancer precludes any normal filtering function and at what point collateral pathways are utilized, so that it no longer has an opportunity for phagocytosis. The few studies that allude to some of these problems are conflicting and do not specifically answer these questions.

The problem of lymphatic pathways in human metastatic cancer is likewise unanswered. Experimental tumors themselves have not been shown to have any lymphatic supply, although the area invaded by the tumor does. Studies on certain metastatic human cancer with various dyes would suggest that this is also true in man. Pilot experiments have shown that although complete replacement of a lymph node by cancer precluded the deposition of radiogold, the presence of only a small amount of lymphoid tissue enabled phagocytosis of radiogold to occur in that portion of the node (2). These findings have recently been confirmed by Seaman and Powers.

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TABLE I.—DISTRIBUTION OF CARCINOMA AND RADIOGOLD IN LYMPH NODES REMOVED FROM SURGICAL SPECIMENS OF 23 WOMEN UNDERGOING RADICAL MASTECTOMY FOR CARCINOMA OF THE BREAST

					Nodes involved by cancer			Nodes uninvolved by cancer		
Patient	*Age, yrs.*	*Millicuries Au^{198}*	*Nodes removed*	*Nodes containing Au^{198}*	*Total*	*With Au^{198}*	*Without Au^{198}*	*Total*	*With Au^{198}*	*Without Au^{198}*
1	53	2.49	18	13	0	0	0	18	13	5
2	57	1.00	9	5	0	0	0	9	5	4
3	45	1.00	18	18	1	0	1	17	17	0
4	59	0.92	4	4	1	1	0	3	3	0
5	53	1.09	7	0	0	0	0	7	0	7
6	64	0.53	16	0	10	0	10	6	0	6
7	56	0.45	24	24	0	0	0	24	24	0
8	64	3.72	23	21	0	0	0	23	21	2
9	44	3.45	15	12	0	0	0	15	12	3
10	48	0.04	20	7	8	2	6	12	5	7
11	50	0.48	19	15	0	0	0	19	15	4
12	43	0.15	13	13	0	0	0	13	13	0
13	37	0.70	16	16	2	2	0	14	14	0
14	54	1.40	15	6	3	3	0	12	3	9
15	55	0.12	12	2	5	2	3	7	0	7
16	48	2.10	23	0	23	0	23	0	0	0
17	60	1.64	27	27	0	0	0	27	27	0
18	38	0.42	21	16	0	0	0	21	16	5
19	50	1.40	27	0	5	0	5	22	0	22
20	62	1.08	23	21	4	2	2	19	19	0
21	48	0.65	20	19	0	0	0	20	19	1
22	45	0.59	21	10	0	0	0	21	10	11
23	45	0.19	18	16	0	0	0	18	16	2

TABLE II.—DISTRIBUTION OF CARCINOMA AND RADIOGOLD IN LYMPH NODES REMOVED FROM SURGICAL SPECIMENS OF 12 PATIENTS UNDERGOING SURGICAL TREATMENT OF CARCINOMA LOCATED IN HEAD OR NECK

							Nodes involved by cancer			Nodes uninvolved by cancer		
Patient	*Age, yrs.*	*Sex*	*Site of primary ca*	*Millicuries Au^{198}*	*Nodes removed*	*Nodes containing Au^{198}*	*Total*	*With Au^{198}*	*Without Au^{198}*	*Total*	*With Au^{198}*	*Without Au^{198}*
1	55	F	Gingivae	1.91	27	11	0	0	0	27	11	16
2	67	M	Tonsil	5.00	19	12	7	5	2	12	7	5
3	47	M	Larynx	0.01	13	5	3	2	1	10	3	7
4	45	M	Larynx	1.18	11	6	7	4	3	4	2	2
5	41	M	Floor of mouth	0.53	24	24	1	1	0	23	23	0
6	51	M	Epiglottis	3.48	16	5	6	2	4	10	3	7
7	48	M	Parotid	0.62	13	3	0	0	0	13	3	10
8	39	M	Floor of mouth	0.17	23	15	0	0	0	23	15	8
9	64	F	Floor of mouth	0.88	3	3	1	1	0	2	2	0
10	39	F	Maxilla (sarcoma)	0.82	21	16	1	0	1	20	16	4
11	54	M	Tongue	0.50	9	5	3	3	0	6	2	4
12	65	M	Tongue	0.19	5	4	3	3	0	2	1	1

A radical neck dissection was performed in conjunction with excision of the primary neoplasm.

It is apparent that more information is requisite before treatment of lymphatic metastases can be intelligently advised. This study was designed to determine the routes of dissemination of interstitially placed radiocolloids in the presence of metastatic cancer and the deposition of the radiocolloid in the lymph nodes containing metastatic cancer.

METHODS

Radioactive gold was considered the most suitable colloid for the purpose of this investigation. As received, it has a particle size of roughly 50 to 100 millimicrons and has been found to follow lymphatic pathways with phagocytosis by reticuloendothelial cells. As supplied, the colloidal solution is sterile, pyrogen-free, and stable no

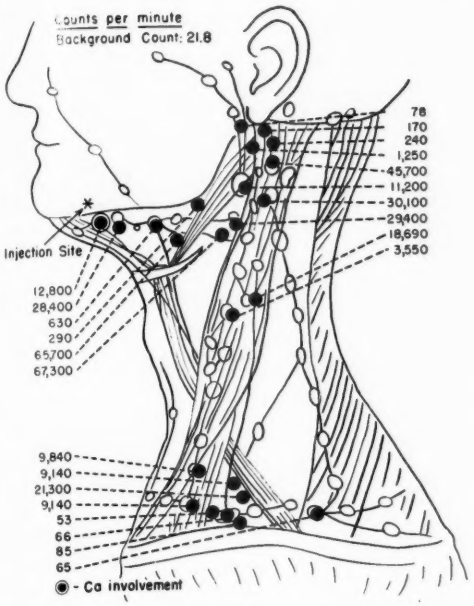

FIG. 1.

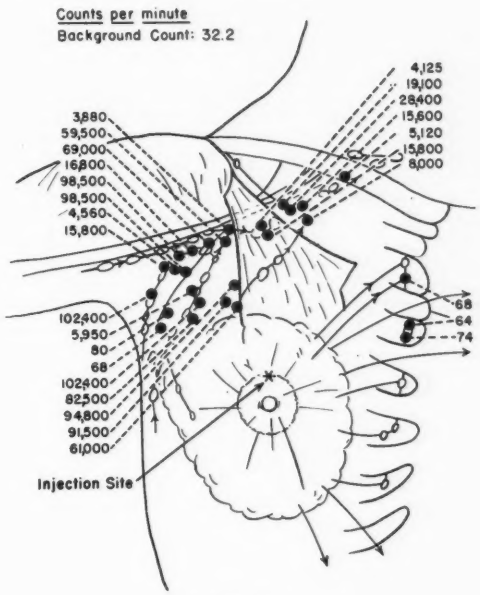

FIG. 2.

FIG. 1. Location and activity of lymph nodes containing radiogold in 41 year old male with carcinoma of floor of mouth. Five-tenths millicurie of radiogold injected in region of carcinoma on March 15, 1954. Excision and radical neck dissection performed on March 18, 1954. Twenty-four lymph nodes were identified with 1 submaxillary lymph node being partially replaced (⅛) by carcinoma. Note variation in activity. The node containing metastatic carcinoma had a count per minute of 12,800.

FIG. 2. Location and activity of lymph nodes from radical mastectomy specimen in 60 year old female receiving 1.64 millicuries of radiogold 24 hours before surgery. Of 27 lymph nodes examined all contained varying amounts of radiogold and none contained cancer.

dilution with procaine. Dilution of the radiogold was carried out with 1 per cent procaine to provide a specific activity of from .1 to 5 millicuries per milliliter. Tracer amounts of radiogold in a volume of 1 milliliter were injected within large tumors[1] or 1 to 2 centimeters from small tumors that were superficially located, such as those originating in the head, neck, or breast. Initially, a dosage of from 2 to 5 millicuries was employed, but it was found possible to procure satisfactory distribution and appraisal with as little as .1 millicurie, and the average dosage varied between .5 and 1 millicurie.

Surgical removal of the primary lesion, including the injection site and regional lymph nodes, was usually carried out within 20 to 24 hours following placement of the radioactive gold. In a few instances, operation was within an hour, and in others was deferred from 72 to 120 hours. Examination of the surgical specimen was performed within 24 hours of its removal, all grossly identifiable lymph nodes being removed by sharp dissection from the fresh specimen. The location of the lymph nodes was plotted on an appropriate diagram and their radioactivity assayed. Activity determinations were made with a gamma sensitive Geiger-Müller tube with a collimated beam. All tissues from the surgical specimen, including those from the region of the injection site, were examined histologically for lymphoid elements, tumor, and relative amounts of each. Dark-field examination of the tissue sections disclosed the location of radiogold

[1]The route of dispersion of radiocolloids from within neoplastic tissue has not been satisfactorily explained.

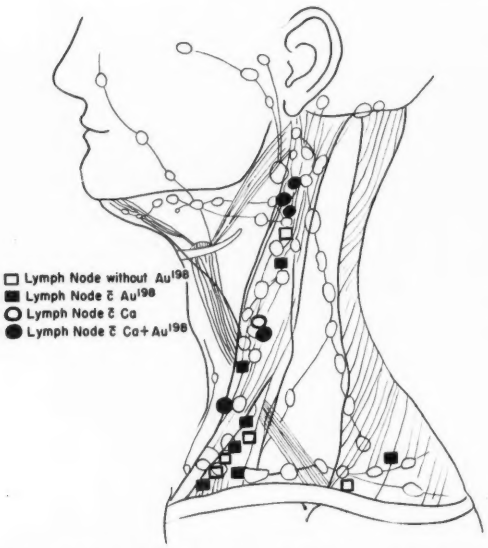

FIG. 3. Distribution of radiogold in a 67 year old male following excision of carcinoma of the tonsil and a radical neck dissection. Five millicuries of radiogold were injected in region of neoplasm 4 days prior to surgery. Note that 2 of 7 carcinomatous nodes and 5 of 12 "normal" lymph nodes did not contain any radiogold. (Patient 2, Table II.)

as highly refractile, spherical, or cylindrical bodies.

OBSERVATIONS

Thirty-five patients proved suitable for study following the interstitial injection of radiogold. Twenty-three of these had carcinoma of the breast (Table I) and 12 had carcinoma originating in the head and neck (Table II).

Five hundred and ninety-three lymph nodes were removed from the surgical specimens of these patients. The criterion for the deposition of radiogold in a lymph node was arbitrarily designated as a count per minute of twice the background. Usually the uptake was several hundred times the background (Figs. 1 and 2) but, with lesser quantities of radiogold employed, lower counts at both injection site and regional lymph nodes were observed. Because of the varying amounts of contained neoplasm, the counts per minute per node were determined, rather than for a specific weight of lymphatic or tumor tissue. Of the 593 lymph nodes examined, 374 contained radiogold and 94 contained cancer. The cancer involvement varied from partial to almost complete replacement of the lymph node. Only 33 of these cancerous lymph nodes also contained radioactive gold. In general within the same specimen, even though radiogold was present in cancerous lymph nodes, considerable more radiogold was present in lymph nodes uninvolved by cancer. Sixty-one of the 94 cancerous nodes failed to disclose any deposition of radiogold. It is evident that frequently the "normal" nodes, that is, those uninvolved by cancer, also did not contain any radioactivity; 159 of the nodes uninvolved by cancer contained no radioactive gold, while 340 uninvolved by cancer contained radioactive gold. This finding was usually associated with the presence of metastatic cancer in other lymph nodes (Fig. 3). With few (less than 3) or no metastases it was customary for most identifiable lymph nodes to contain deposits of radiogold (Tables I and II).

Histologic examination of cancerous lymph nodes without radiogold disclosed a few with complete replacement by tumor and little or no identifiable lymphatic tissue. Many of the cancerous nodes, however, had large amounts of lymphoid elements remaining but no radioactivity. In those nodes containing radioactivity and metastatic cancer, dark-field studies disclosed a very striking deposition of gold particles in the reticuloendothelial cells (Fig. 4). The gold was confined to those areas of the lymph node containing lymphoid elements. In several instances, only a rim of lymphatic tissue remained but this disclosed intense radioactivity (Figs. 5 and 6). Apparently, if lymphatic channels are still patent, remaining lymphoid elements are capable of function. Occasionally, despite what appeared to be near replacement of portions of a lymph node by tumor, radiogold could be identified within tumor tissue. This was a very unusual finding and was interpreted as gold

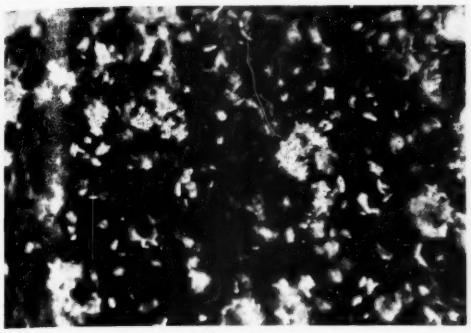

FIG. 4.

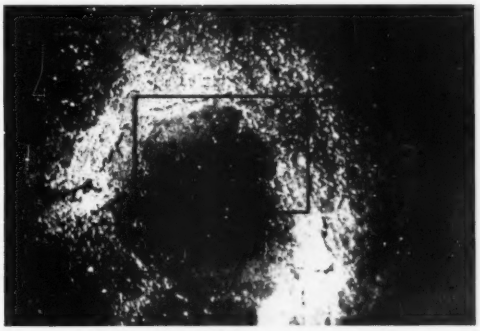

FIG. 5.

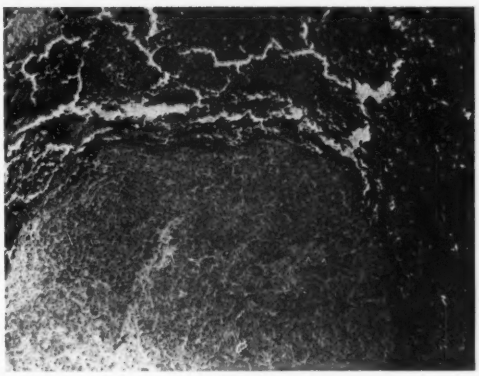

FIG. 6.

FIG. 4. Photomicrograph of dark-field examination of carcinomatous node containing radiogold. ×332. Highly refractile radiogold appears as small rods appearing singly and in clusters.

FIG. 5. Photomicrograph of dark-field exposure of lymph node containing cancer and radiogold. Tumor in center (see Fig. 6) is encircled by highly refractile radiogold. Such a metastasis could theoretically be destroyed by the surrounding radiocolloid. ×24.

FIG. 6. Area outlined in Figure 5. Squamous carcinoma is partly encircled by lymphoid elements. ×77.

particles in reticuloendothelial cells rather than in tumor cells or lymphatic pathways.

DISCUSSION

These findings demonstrate that in the patient uninvolved by metastatic neoplasm interstitial injection of radiogold is followed by immediate dissemination throughout the regional lymph nodes without appreciable "filtering" by proximal nodes. This distribution of gold particles suggests direct passage through a lymph node, because of particle size, or passage through collateral channels. Such uniformity of distribution could not be procured in patients with metastatic carcinoma.

Two factors would seem to militate against the effective treatment of carcinomatous nodes by radiocolloids. In the presence of metastatic cancer there is apparently some alteration in "normal" lymphatic flow as measured by radiogold deposition. As a result, there is no uniform distribution of radiogold even in those lymph nodes uninvolved by neoplasm. Secondly, and of greater importance, is the failure of gold to be deposited in most lymph nodes containing cancer. From studies of these lymph nodes with the dark-field microscope human cancer does not appear to contain functioning lymphatic channels and, therefore, in such nodes lymphoid tissue appears to be essential for a carcinomatous node to phagocytize radiogold. The greater the replacement of the node by tumor, the less likely the deposition of gold colloids.

It is conceivable that if the lymph node metastasis were small (less than twice the tissue penetration distance of the beta ray) and partially surrounded by lymphoid tissue (e.g., Figs. 5 and 6) destruction of the lymph node and contained neoplasm could be accomplished by necrotizing doses of radiogold. However, early in the disease, this type of metastasis would most likely be present in the lymph nodes contiguous to the neoplasm. These are also the lymph nodes that are most accessible to surgical excision. Car-

cinomatous involvement of more distant lymph nodes (those presumably inaccessible to surgical removal but possibly reached by lymphatically disseminated radiocolloids) does not usually occur until the more proximal nodes already contain metastatic cancer. This observation has been nicely demonstrated in the experimental animal, in which the first lymph node encountered will usually serve as an effective barrier against further lymphatic dissemination of tumor for approximately 3 weeks. Therefore, even though the more distant and surgically inaccessible lymph nodes were to contain only small deposits of metastatic neoplasm, it appears unlikely that the lymphatic distribution of the radiocolloids would be sufficiently uniform to result in destruction of these lymph nodes. Once metastases to proximal nodes occur, the route of lymphatic dissemination of radiocolloids is unpredictable.

Although only tracer amounts of radiocolloids were used, it would seem doubtful that the distribution pattern with therapeutic amounts would be much altered.

SUMMARY

Tracer amounts of radiogold injected interstitially within or near externally situated malignant neoplasms disseminate rapidly by way of the lymphatics to be phagocytized by functioning lymphoid elements of regional lymph nodes. Lymphatic tissue is essential for the deposition of radiogold in a cancerous lymph node. However, even with lymphoid elements present, most cancerous lymph nodes do not sequester radioactive colloids. Furthermore, lymph node metastases may so alter lymphatic flow that not only is there interference with the deposition of radiogold in carcinomatous nodes, but there is also less deposition in nodes uninvolved by tumor.

On the basis of these studies, successful treatment of metastatic carcinoma by lymphatic dissemination of radioactive gold colloids would not only appear to be unlikely, but such an attempt would possibly be hazardous, because of the dissemination of the radioactive material to unpredictable sites.

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PASTEURELLA INFECTION FROM CAT BITES

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PASTEURELLA MULTOCIDA is a small gram-negative, nonmotile, bipolar staining bacteria which causes hemorrhagic septicemia in many animals. It has been given various names, such as Pasteurella avicida, Pasteurella boviseptica, Pasteurella lepiseptica, and Pasteurella suiseptica, depending upon which animal has been involved. However, recent bacteriologic studies have revealed these strains to be nearly identical and the name Pasteurella multocida has been adopted for all of them.

Human infections with this organism consist of a systemic form with no known portal of entry and a localized form resulting from animal bites. A rare meningitic form follows trauma to the face and head suggesting that this organism is commensal in the nasal cavities.

The systemic form presents a wide variety of clinical processes such as bronchiectasis, sinusitis, meningitis, brain abscess, empyema, and fulminating septicemia. The first human systemic infection, which was well documented by bacteriologic studies, was reported by Hundeshagen during the 1919 influenza pandemic. Cases, which were reported previous to this, lacked complete bacteriologic studies. Prior to 1947, this disease appeared to be confined to the Old World, but since then 45 cases have been reported from the United States. An additional case was reported but must be eliminated since it does not meet rigid bacteriologic criteria.

Localized infection following an animal bite was first reported by Kapel in 1930 (6, 7). Twenty-two additional cases have been reported to date. The cat is the most frequent offender but other animals such as the dog, rat, rabbit, and panther have been involved.

The pattern of infection following an animal bite is a localized pyogenic reaction. Soon after the bite the area becomes painful, red, tender, and markedly edematous, with an ascending lymphangitis and lymphadenitis. In the absence of antibiotic therapy an abscess almost always develops at the site of bite which heals slowly for weeks to months.

Since osteomyelitis frequently occurs, it has been suggested that this organism has a propensity for bone involvement. However, we believe the organism has no special affinity for bone, but the sharp needle-like cat fangs predispose to placing the organism on the surface or within the substance of the bone. The dog fang is much blunter than that of the cat, and osteomyelitis is seldom seen with such bites. The fangs of the rat are blunt and short, and no cases of osteomyelitis have been reported following such bites. Rabbit fangs are also blunt and, in 1 case of wound infection following this type of bite, no bony involvement occurred.

This infection is probably more common than the sparsity of case reports would indicate. Less serious grades of the infection and those modified by antibiotics probably go unrecognized. In the more serious forms this gram-negative organism is probably overlooked or reported as some other organism. We are presenting 3 recent cases of Pasteurella multocida infection seen at the Boston City Hospital following cat bites in order to alert other physicians to the possibility of this infection.

CASE REPORTS

CASE 1. L. G., a 73 year old white female, was admitted to the Boston City Hospital on June 11, 1955,

From the Third (Boston University) Surgical Research Laboratory and the Mallory Institute of Pathology, Boston City Hospital.

TABLE I.—PASTEURELLA STRAINS

Strain No.	*Source*
19963	Case 1 (L.G.) Boston City Hospital
28910	Case 2 (A.J.) Boston City Hospital
25027	Case 3 (L.A.) Boston City Hospital
11039	American Type Culture Collection
3072	Denmark State Serum Institute
5691	Denmark State Serum Institute
3615	Denmark State Serum Institute
27405	Throats of healthy cats
27406	Throats of healthy cats
27409	Throats of healthy cats

with the chief complaint of a tender swollen left hand. Two days prior to admission the patient was scratched and bitten by a cat, sustaining full thickness lacerations and puncture wounds of the left hand and wrist. One day prior to admission the hand became painful and swollen and the patient instituted treatment with chlorazine soaks. The swelling and pain increased and was associated with erythema which spread up the anterior surface of the forearm.

Physical examination revealed a temperature of 100 degrees, pulse 90, respirations 24. There was marked swelling, redness, and tenderness of the left hand extending to the elbow on the anterior surface of the forearm.

The patient was treated with elevation of the extremity, warm wet packs, aqueous penicillin (100,000 units q.i.d.) and prophylactic tetanus antitoxin. No roentgenograms were taken. By the seventh hospital day the patient had become afebrile. An ulcer developed on the thenar eminence, measuring 3 millimeters in diameter, which drained a small amount of purulent material. The next day the patient was discharged to the out-patient department.

Five days after discharge, roentgenograms were taken, because of persistent pain and drainage, which revealed osteomyelitis of the first metacarpal and greater multangular bone (Fig. 1). The patient was readmitted to the hospital where physical examination revealed a deep ulcer on the thenar eminence with surrounding erythema and crepitation on moving the first carpometacarpal joint. Treatment consisting of hot wet packs and elevation of the extremity was instituted. On the second hospital day a longitudinal incision was made over the site of drainage at the carpometacarpal joint and carried down to bone with removal of a sequestrum. The wound was packed open with vaseline gauze and the hand and forearm were immobilized in plaster with the hand in a position of function.

The culture was reported as an atypical Bacillus proteus, resistent to penicillin and streptomycin, but sensitive to tetracycline and chloramphenicol. The patient was treated with tetracycline for 8 days, receiving 500 milligrams every 6 hours. She became afebrile and the wound healed rapidly with complete return of function 26 days after the incision and drainage.

The association of cat bite with the rapid dissolution of bone was suggestive of a case report by Kapel (5). Further bacteriologic studies were initiated which revealed that the organism previously called atypical Bacillus proteus was really a member of the genus Pasteurella. This was the first instance in which this organism was reported from the Boston City Hospital Bacteriological Laboratory (8).

CASE 2. A. J., a 68 year old diabetic female, was admitted to the hospital on September 3, 1955, with the chief complaint of pain, redness, and swelling of the left ankle of 3 weeks' duration. Seven weeks prior to admission the patient had been bitten and scratched by a cat, sustaining 3 broken areas in the skin overlying the left ankle, 2 of which did not heal. The ankle gradually became red, painful, and swollen.

Physical examination revealed a temperature of 99.4 degrees and pulse 110. There was erythema,

TABLE II.—CULTURAL CHARACTERISTICS

	Pasteurella Strain No.									
	27406	*27409*	*27405*	*3615*	*5691*	*3072*	*11039*	*25027*	*28910*	*19963*
Hemolysis	0	0	0	0	0	0	0	0	0	0
Bipolarity	+	+	+	+	+	+	+	+	+	+
Indole production	+	+	+	+	+	+	+	+	+	+
Carbohydrate fermentation reactions										
Dextrose	+	+	+	+	+	+	+	+	+	+
Mannite	+	+	+	+	+	+	+	+	+	+
Saccharose	+	+	+	+	+	+	+	+	+	+
Sorbitol	+	+	+	+	+	+	+	+	+	+
Rhamnose	0	0	0	0	0	0	0	0	0	0
Arabinose	0	+	0	0	+	0	0	0	0	0
Xylose	+	+	0	+	+	+	0	+	+	+
Maltose	0	0	+	0	+	0	0	0	0	0
Salicin	0	0	0	0	0	0	0	0	0	0
Dulcitol	0	0	0	0	0	0	+	0	0	0
Methyl red	0	0	0	0	0	0	0	0	0	0
Voges-Proskauer	0	0	0	0	0	0	0	0	0	0
Hydrogen sulfide production	0	0	0	0	0	0	0	0	0	0
Methylene blue reduction	+	+	+	+	+	+	+	+	+	+

0—Negative
+—Positive or acid

swelling, and tenderness over the lateral aspect of the left foot with purulent drainage extending from 2 sinus tracts in the area.

Urinalysis, on admission, revealed 4 plus glycosuria and 3 plus ketonuria. The fasting blood sugar was 297 milligrams per cent; white blood count, 13,450. X-ray films of the foot were negative for osteomyelitis. Treatment consisted of elevation of the extremity, warm saline soaks, procaine penicillin (600,000 units b.i.d.) and gantrisin in full dosage.

On the second hospital day the patient was taken to the operating room where the abscess over the lateral aspect of the ankle was incised and packed open. Following this the patient became afebrile. The diabetes was regulated with 35 units of NPH insulin daily. The wound required 4 weeks for complete healing.

CASE 3. L. A., a 16 year old white male, was admitted to the Boston City Hospital on August 16, 1955, with a chief complaint of an infection of the wrist of 1 week's duration. One week prior to admission, while at work in an animal hospital, the patient was bitten on the ulnar aspect of the left wrist by a jaundiced cat that died prior to the patient's admission to the hospital. The day following the bite the patient was given prophylactic tetanus antitoxin and the wound was cleansed and dressed. During the next 4 days the hand was red and swollen but 2 days before admission, the patient inadvertently struck it and the swelling, pain, and tenderness increased. Twenty-four hours prior to admission a culture was taken, and he received 300,000 units of procaine penicillin.

Physical examination revealed a draining wound of the dorsum of the left wrist. This draining wound was surrounded by a 4 centimeter zone of erythema and tenderness.

The hand and wrist were immobilized in a position of function with massive wet packs. Roentgenograms of the hand and wrist were negative for bone disease. The wound healed within 5 days without any complications.

BACTERIOLOGIC STUDIES

Complete bacteriologic studies were made on the organisms isolated from the 3 cases reported in this paper. They were compared with known strains of Pasteurella obtained from the American Type Culture Collection and with 3 known strains obtained from the Statens Seruminstitut (Copenhagen, Denmark). In addition, Pasteurella strains were obtained from cats studied at the Animal Rescue League of Boston. The source from which the Pasteurella strains were obtained may be seen in Table I.

FIG. 1. X-ray film of left wrist 14 days after cat bite demonstrating osteomyelitis of greater multangular and base of first metacarpal bones.

CULTURAL CHARACTERISTICS (TABLE II)

Hemolysis. All strains were incubated on agar plates containing 10 per cent sheep's blood for 48 hours and none produced hemolysis.

Bipolarity was observed in all strains in smears of 18 hour broth cultures stained for 2 minutes with methylene blue.

Indole production from 1 per cent tryptone, incubated for 24 hours, was found in all strains.

Catalase was demonstrated by the release of oxygen from a strong hydrogen peroxide solution poured over an 18 hour culture on a plain agar slant in all strains.

Fermentation reactions. All strains produced fermentation with dextrose, mannite, saccharose, and sorbitol. No strains produced fermentation with rhamnose or salicin. Two strains fermented maltose. Fermentation tests with arabinose, xylose, and dulcitol revealed 6 of the strains to be in the Rosenbusch-Merchant group 2, i.e., fermenting xylose but not arabinose and dulcitol. The

TABLE III.—VIRULENCE STUDIES

Pasteurella Strain No.	*Dilution*	*Hours of life after injection*	*Pasteurella Strain No.*	*Dilution*	*Hours of life after injection*
19963	$1:10^2$	14	5691	$1:10^2$	22
	$1:10^4$	20		$1:10^4$	23
	$1:10^6$	28		$1:10^6$	Lived 30 days
28910	$1:10^2$	18	3615	$1:10^2$	14
	$1:10^4$	48		$1:10^4$	14
	$1:10^6$	18		$1:10^6$	14
25027	$1:10^2$	4	27405	$1:10^2$	44
	$1:10^4$	7		$1:10^4$	115
	$1:10^6$	24		$1:10^6$	Lived 30 days
11039	$1:10^2$	7	27409	$1:10^2$	21
	$1:10^4$	7		$1:10^4$	21
	$1:10^6$	14		$1:10^6$	27
3072	$1:10^2$	22	27406	$1:10^2$	18
	$1:10^4$	21		$1:10^4$	17
	$1:10^6$	21		$1:10^6$	49

Heart-blood cultures were positive for Pasteurella multocida in all mice which died following intraperitoneal injections.

other 4 strains, however, could not be classified in the Rosenbusch-Merchant group 1 (fermenting arabinose and dulcitol but not xylose) since there was no consistency of fermentation.

Methyl red. The methyl red test was negative for all strains.

Voges-Proskauer tests were performed on 18 hour cultures by adding 3 milliliters of a 5 per cent alcoholic solution of alphanaphthol and 1 milliliter of strong sodium hydroxide (saturated). All strains were negative.

Hydrogen sulfide production by incubating the strains on Kligler's iron agar for 48 hours was not present in any strain.

Methylene blue reduction gave a positive reaction in all strains.

VIRULENCE STUDIES (TABLE III)

All strains were tested for pathogenicity in mice. Serial dilutions with beef broth were made of 18 hour cultures of each of the 10 strains, and 0.5 milliliter of each dilution was injected intraperitoneally in mice who were observed at 4 hour intervals until the time of death. Immediately upon death the mice were autopsied and heart-blood cultures were taken by first searing the apex of the heart, amputating it with a sterile scissors, and inserting a sterile wire loop into the heart chamber. This was immediately streaked on a blood agar plate and incubated into beef broth.

The mice dying within 12 hours showed no gross pathologic abnormality. Those dying in from 12 to 18 hours revealed a mild serous peritonitis. Those living longer revealed a plastic fibrinous peritonitis and a serous pleuritis. Animals that survived longer than 24 hours but died of infection also exhibited scattered petechial hemorrhages in the lungs and occasionally in the abdominal viscera.

All the strains showed marked pathogenicity to mice even in a dilution of $1:10^6$ power, except for strains 5691 and 27405 which lived for 30 days. In the dilutions below this, all the strains were markedly pathogenic for the mice.

TABLE IV.—ANTIBIOTIC SENSITIVITY STUDIES

Pasteurella Strain No.	*Erythromycin*	*Penicillin*	*Chlortetracycline*	*Chloramphenicol*	*Streptomycin*	*Polymixin*
19963	3.1	0.39	3.1	3.1	25.0	12.5
28910	3.1	0.39	1.5	3.1	25.0	12.5
25027	3.1	0.39	1.5	1.5	6.2	6.2
11039	3.1	0.39	1.5	1.5	25.0	12.5
3072	3.1	0.39	1.5	1.5	25.0	12.5
5691	1.5	0.39	0.78	1.5	12.5	12.5
3615	6.2	0.39	1.5	3.1	12.5	3.1
27405	3.1	0.19	0.78	1.5	6.2	0.39
27409	3.1	0.39	1.5	3.1	25.0	6.2
27406	3.1	0.39	1.5	3.1	25.0	3.1

Minimum inhibiting concentration expressed in micrograms per milliliter.

ANTIBIOTIC SENSITIVITY STUDIES (TABLE IV)

Sensitivity studies were performed by streaking 18 hour blood broth cultures on 10 per cent horse blood agar plates containing various concentrations of different antibiotics which were incubated for 48 hours at 37 degrees C. The minimum inhibiting concentration is the smallest amount of antibiotic per milliliter which will totally inhibit growth of the organism under study. All the strains were completely sensitive to penicillin, chlortetracycline, chloramphenicol, and erythromycin. In general, these results are comparable to those of Neter and Gorzynski (1–3, 9).

TREATMENT

Cat bites seen initially should receive a thorough soap and water scrub followed by a saline irrigation and sterile dressing. Pro-

phylactic tetanus antitoxin or toxoid injections are important, and procaine penicillin (600,000 units) should be administered daily for 4 days. The patient should be observed closely but may be treated as an out-patient. Primary excision of the wound has been suggested but hardly seems necessary in view of this organism's sensitivity to penicillin.

If the wounds are seen after infection has developed, the patient should be admitted to the hospital and roentgenograms obtained, since osteomyelitis may be apparent as early as 12 days after the bite. Cultures of the wound should be taken with special note made of the possibility of infection with Pasteurella multocida. Unless this is done, there is always the possibility that these infections will pass unnoticed. Penicillin therapy should be given while waiting for the results of culture and sensitivity studies. Since an occasional clinical case may be resistant to penicillin, careful appraisal of the sensitivity studies should be made in choosing the proper antibiotic. Osteomyelitis should be surgically incised, since failure to do this has resulted in a prolonged course with permanent disability in many instances. However, an open mind should be kept on this matter in view of the organism's sensitivity to penicillin.

SUMMARY

The relationship of Pasteurella multocida infection to animal bite in general and cat bite in particular has been emphasized. Three new cases of this infection following cat bite with detailed bacteriologic studies of the isolated strains have been presented, bringing the total number of recorded cases of this disease to 26.

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FRACTURE OF THE FEMORAL NECK FOLLOWING IRRADIATION OF THE PELVIS

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ALTHOUGH CERTAIN ETIOLOGIC FACTORS leading to necrosis or pathologic fracture of bone following roentgen irradiation are now better understood and controlled, this condition still remains a complication of treatment in a few cases. The apparent increase in the number of cases of fracture of the femoral neck following irradiation of the pelvis is probably the result of improvement in diagnosis rather than any actual increase in incidence. With improvement in irradiation technique, the incidence of femoral neck fracture, previously reported as occurring in about 2 per cent of all patients receiving roentgen irradiation for pelvic cancer, may be expected to decrease. A study of the results of treatment in a group of 9 cases of femoral neck fracture indicates that methods of treatment of this complication can be improved.

Postirradiation fracture of the femoral neck has been reported as healing without any specific treatment other than protection from weight bearing. However, one would hardly be justified in recommending this course of treatment as a routine, as some fractures so treated have failed to unite. Methods of treatment advised have been many and varied. Among those suggested have been fixation with nails or pins, bone grafting, spica cast, McMurray osteotomy, fusion, excision of femoral head, Colonna reconstruction procedure. In most references, the method of treatment has been mentioned only incidentally to a description of the occurrence of this pathologic fracture. A review of these various methods of treatment suggests that all were not well planned and that a method that might be indicated in certain of these cases was not indicated in the individual case described. It is clear that optimum results in treatment can be gained only if this complication is recognized and diagnosed correctly early. The diagnosis will be made early only if the possibility of this fracture is kept in mind in all patients who complain of pain in the hip or knee following irradiation for pelvic cancer. Early roentgenograms commonly fail to show a fracture of the femoral neck, but subsequent films taken several weeks later will show the fracture line. If the patient has been prevented from bearing weight on the affected leg, little deformity will be present and internal fixation can be accomplished with successful union almost always assured. If the limb is not protected from weight bearing, deformity will result requiring reduction as well as fixation of the fracture.

CASE 1. M. P. This patient, a 54 year old white female, was admitted to the hospital on November 29, 1949 with a fracture of the neck of the left femur. In October 1948, she had received 6,000 milligram hours of radium for carcinoma of the cervix of the uterus and later a total of 8,400 roentgens of roentgen irradiation delivered through 4 ports. Roentgenograms showed a typical spontaneous frature of the left femoral neck (Fig. 1). On November 30, 1949, after the hip had been reduced openly, it was fixed by the use of a Smith-Petersen nail. Histologic study of a section of bone taken from the region of the fracture failed to show any carcinoma metastasis. Convalescence after pinning was uncomplicated. She was started on partial weight bearing 8 months after operation and gradually carried to full weight bearing (Fig. 2). When last seen in December 1951, she was walking without pain or limp and union appeared solid.

To avoid possible dislodgement of the head when inserting the Smith-Petersen nail, some have preferred the use of multiple pins of the Austin Moore type.

CASE 2. M. E. A 57 year old white female was admitted to the hospital on September 3, 1954 complaining of hip pain of 3 weeks' duration. Nine months previously she had been treated for a stage 2 carcinoma

of the cervix with intravaginal radium and roentgen irradiation of 18,500 roentgens given through 14 ports. Roentgenographic examination (Fig. 3) revealed a subcapital fracture in the typical varus position that Smith has described. With light traction, this fracture was corrected, and to avoid displacement multiple pins of the Austin Moore type were used for fixation (Fig. 4).

Of the 9 cases of femoral neck fracture following pelvic irradiation treated in the years from 1949 through 1954, 5 were treated by internal fixation after reduction. All later showed satisfactory bone healing.

Because of early necrosis of the femoral head, seen at the time the fracture was first recognized, another method of treatment would seem to be demanded. For these some type of femoral head prosthesis has been used.

CASE 3. C. J. A 60 year old negress was admitted to the hospital on April 7, 1952 because of pain in the right hip region. From September to November 1950 she had been treated for a stage 4 squamous cell carcinoma of the cervix with extensive pelvic infiltration. The amount of irradiation received was: (1) radium implantation in the parametrium, a total of 30,500 gamma rays; (2) roentgen irradiation, 3 posterior portals 2,800 roentgens, 3 anterior portals 3,000 roentgens each, and a single intravaginal portal of 2,400 roentgens.

Roentgen examination of the hip revealed extensive necrosis of the femoral head (Fig. 5). The usual nailing procedure was not indicated and a femoral head prosthesis of the Judet type was inserted (Fig. 6). Postoperative, because of general debility, it was never possible to ambulate her, but it was possible to get her into a wheelchair. She died in a convalescent home 6 months following her discharge from the hospital.

FIG. 1. Varus position of fragments following spontaneous fracture.

In this case diagnosis of the fracture was not made until 7 months after the first complaints of pain in the hip. Optimum results in treatment can never be achieved with such delay. A similar delay and result were seen in 2 other cases.

In 1 other case the process of necrosis did not proceed to include the entire head.

CASE 4. R. M. A 51 year old white female was first admitted to the hospital in December 1953. In 1950, at

FIG. 2. Eight months following open reduction and nailing.

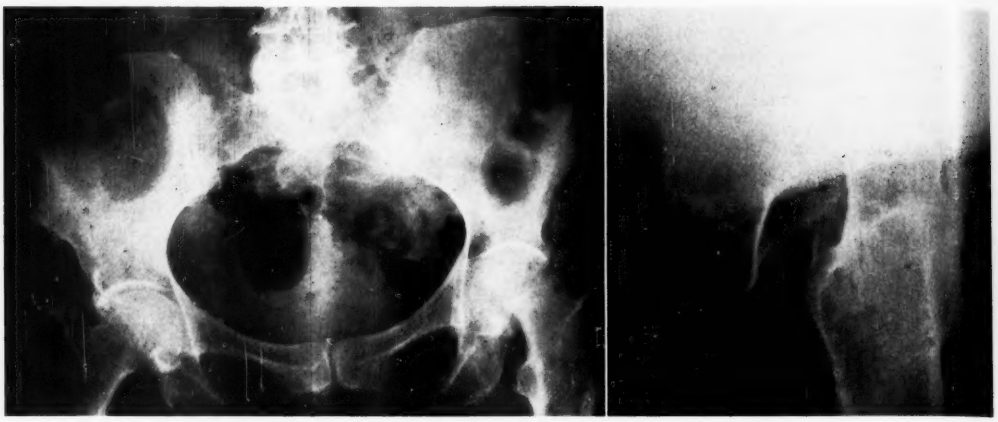

FIG. 3. Case 2. Typical position of head following spontaneous fracture.

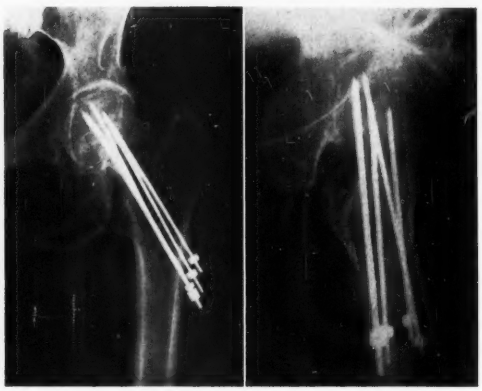

FIG. 4. Case 2. Reduction by straight traction and fixation with multiple pins.

another hospital, she had had radium implantation and roentgen irradiation for carcinoma of the cervix. The exact amount of irradiation is not known. She first complained of pain in the left hip in April 1953 and when seen here 8 months later she had a severe limp on the left side. The hip was held in 25 degrees flexion and 15 degrees' adduction with only a few degrees of painful motion demonstrable from this position. Roentgen examination revealed a segmental aseptic necrosis of the femoral head (Fig. 7). On February 19, 1954, a Whitman reconstruction of the hip was performed. Convalescence was uncomplicated and ambulation was started 8 weeks after operation. When seen a year later she walked with some limp but demonstrated 90 degrees of motion in flexion-extension, 15 degrees of abduction, and 10 degrees of rotation (Fig. 8).

The exact effect of roentgen irradiation of bone is not clearly understood. No completely satisfactory explanation can be given as to why one patient develops aseptic necrosis or spontaneous fracture after deep roentgen irradiation while another who has received a similar dosage reveals no bone change. It is difficult to explain why necrosis and fracture occur in one femur only, although an identical dosage of roentgen rays was administered to both sides of the pelvis.

MacDougall and associates and Bonfiglio have described the pathologic changes that take place. The most important change is that of osteoporosis of the femoral neck. Some bone trabeculae appear eroded and osteoblasts are absent. Apparently, in the usual patient with an irradiation fracture, the amount of irradiation received is below that amount necessary to cause complete necrosis. The subcapital zone of osteoporosis so weakens this area of support that the usual stress of weight bearing is enough to cause the fracture. In such a case adequate callus and repair occurs at the fracture site. When complete necrosis of the head occurs, it must be assumed that the dosage received is greater causing thinning of bone trabeculae, endarteritis, and interference with the usual picture of bone repair. Slaughter has estimated the average dose to the head and neck at 3,000 roentgens. The tolerance dose of the femoral head and neck has been estimated at 3,840 to 4,320 roentgens. That amount of

FIG. 5.

FIG. 6.

FIG. 7.

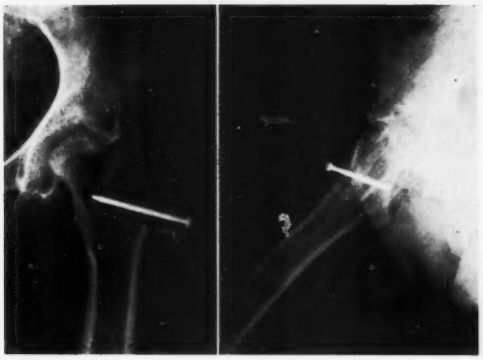

FIG. 8.

FIG. 5. Case 3. Spontaneous fracture with extensive necrosis of the femoral head.

FIG. 6. Case 3. Prosthetic replacement of femoral head. Patient recovered a very satisfactory range of motion and was comfortable but never able to bear weight on this extremity.

FIG. 7. Case 4. Segmental necrosis of the femoral head following irradiation.

FIG. 8. Following Whitman reconstruction procedure.

radiation is said to produce temporary to prolonged inactivation of bone regeneration.

In the 3 cases of our group that showed femoral head necrosis requiring prosthetic replacement, delay in diagnosis ranged from 5 to 9 months. In the other cases in which we were able to use internal fixation of the fracture, this delay in diagnosis was not present, so that we believe this factor as well as that of total irradiation to be important. Internal fixation following early diagnosis resulted in healing and a completely satisfactory hip. Delay in diagnosis in our experience has meant necrosis of the femoral head with the final results of treatment less than satisfactory.

CONCLUSIONS

1. The incidence of femoral head fracture following pelvic irradiation for carcinoma has been reported as varying between 1 to 2 per cent of cases. This incidence is high enough to suspect any person who complains of hip pain following such treatment to have a fracture of the femoral neck. The fracture may not be apparent on the first roentgen examination and be seen a few weeks later.

2. The results of treatment after early diagnosis are superior to those after delayed diagnosis.

3. In those cases in which femoral head necrosis has supervened, the choice of reconstruction procedure will depend on factors presented by each case and should be carefully reviewed if the maximum in rehabilitation is to be achieved.

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ANEURYSMAL BONE CYST

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ANEURYSMAL BONE CYST is a peculiar and somewhat uncommon osseous lesion first described by Jaffe and Lichtenstein in 1942 about which there still exists a considerable degree of confusion in spite of the well established clinical, radiologic, and pathologic, features.

The lesion consists of a cystic cavity destroying the cortex of a bone eccentrically and lined by a mesh of fibrous tissue and vascular spaces containing liquid, nonstagnant blood. In most cases the amount of tissue is scarce but the lesion attains a considerable size, causing a characteristic blown-out effect into the soft tissues adjacent to the affected bone. This mass, being subperiosteal, appears surrounded by a thin shell of new bone, giving the lesion a rather specific radiologic appearance.

Prior to Jaffe's description, there have been cases described in the literature under many different names. As early as 1891, Van Arsdale reported 1 such instance, although he attributed it to an ossifying subperiosteal hematoma resulting from trauma to the midshaft of a femur. Bloodgood, in 1910, similarly attributed the lesion to a subperiosteal hematoma with formation of a peripheral bone shell.

Cone reported on the histology of the lesion and was the first one to call attention to the nonstagnant blood contained in the dilated vascular spaces, thus making the first attempt to differentiate it from true ossifying hematoma.

Geschickter and Copeland were attracted by the presence of giant cells and classified this lesion as a subperiosteal giant cell tumor, a term which attained wide acceptance.

Coley and Miller, remarking on the rather benign course and the clinical differences of this lesion as to location and age group distribution, classified it as atypical giant cell tumor.

However, Jaffe and Lichtenstein were the first to report this lesion as an "aneurysmal bone cyst" for they recognized that it was not actually related to giant cell tumor. This descriptive term calls attention to the lesion's main characteristics and does not lend itself to confusion as did the term "benign bone aneurysm" proposed by Ewing, since we know now that the supposed malignant counterpart or "malignant bone aneurysm" is truly a large, pulsating, usually rather aggresive type of giant cell tumor that produces a thrill to auscultation because of its large arteriovenous communications.

ETIOLOGY

The etiology of aneurysmal bone cyst is still unknown. Jaffe and Lichtenstein agree that there is an underlying, localized vascular condition, which results in marked increase in venous pressure in a segment of a bone, accounting for the destruction that results, and that as the lesion progresses and enlarges an attempt at repair is made thus producing the rim of periosteal new bone and the production of giant cells and fibrous tissue. Lichtenstein goes further to suggest that the vascular condition responsible may be in the nature of venous thrombosis or arteriovenous communication, but to us this seems speculative.

The role of trauma. Thompson, in 1954, reported that in 61 per cent of the cases in the literature, there was a history of trauma. He went further to suggest that the rupture of nutrient vessels with resulting hematoma and attempt at repair might well account for the origin of the lesion. On the other hand, a history of trauma was lacking in 6 of his own series of 9 cases. As the number of

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FIG. 1. FIG. 2.

FIG. 1. Case 1. Aneurysmal bone cyst of midportion of femur in an adolescent. Note the typical blown-out appearance.

FIG. 2. Case 1. Same case. Showing healed cyst 18 months later.

reported cases increases there is growing evidence that trauma plays no other role than to call attention to a pre-existing lesion.

Age, sex, and location. Aneurysmal bone cyst is found more frequently in infants, children, and young adults. The majority occur between the ages of 10 and 20 years. The youngest patient of our series was 9 years old and the oldest 44.

Sex appears to play no part in this condition, the incidence being about equal for both sexes. In our series there were 9 males and 11 females.

While examples have been reported in nearly every bone in the skeleton, the lesion shows a marked predilection for the long bones and the vertebrae which together account for 75 per cent of the cases. The distribution in our series was as follows: the pubis in 4 cases, the tibia in 3, the femur in 2, the lumbar vertebrae in 2, the ilium in 2, and the sacrum, humerus, fibula, radius, clavicle, metatarsal, and the os calcis in 1 case each.

SYMPTOMS

The symptoms are usually insidious and of several months' duration, consisting of mild pain slightly aggravated by activity and progressive swelling. If the lesion is located near a joint, some disability and impairment of function may be present; if superficially located, the patient may be aware of a hard mass attached to a bone gradually increasing in size. There is no pulsation on palpation.

When the vertebrae are involved there may be signs and symptoms of cord or root pressure ranging from mild paresthesia to a severe degree of paralysis. Because of the insidious nature of this lesion it has usually attained a considerable size by the time medical advice is sought. Pathologic fracture may occur as in the majority of other lytic bone lesions but it has been mentioned only once in the cases reported in the literature.

ROENTGENOLOGIC APPEARANCE

When the lesion is located in the long bones it presents its most characteristic features. It generally affects the proximal or distal diaphysis. It seldom involves the epiphysis, except secondarily in neglected cases. It presents a cystic cavity destroying the cortex as evidenced by the fuzziness of the contour and lack of continuity. This condition is associated with an expansile, denser-than-water mass which protrudes eccentrically into the adjacent soft tissues. The rim of this mass is lined by a shell of periosteal new bone measuring a few millimeters in thickness. This is the typical, so-called blown-out pattern of which there may be several variants. For example, even in the long bones, cases have been observed in which the lesion was more or less central and had caused a fusiform expansion of the bone with destruction of the cortex on both sides. In the vertebral column, any portion, including the sacrum may be affected. The lesion may be seen destroying the spinous process, the neural arch, or the body of one or several adjacent vertebrae. In this loca-

tion, as in the flat bones, the appearance of the lesion may be modified to a certain extent by the local anatomy but there is usually enough of a soft tissue shadow with its characteristic bone rim extruding into the adjacent tissues to permit accurate diagnosis in most instances. Roentgenologically, the process might occasionally be mistaken for juvenile bone cyst, since the location and age group distribution are similar. When the lesion is bulky and there is enough spontaneous attempt at repair, some trabeculation and "soap-bubble" appearance may be present thus simulating the roentgenologic appearance of a giant cell tumor. However, in the latter condition the trabeculation is as a rule more uniform, the location is mainly epiphyseal, and these tumors do not occur in children. Also, giant cell tumors are extremely rare in the vertebrae, one of the favored locations for aneurysmal bone cysts. Nonosteogenic fibroma may at times be a cause of confusion but it lacks the soft tissue mass and the blown-out effect. Another condition which has been reported as simulating aneurysmal bone cyst is the telangiectatic form of osteogenic sarcoma, and mistakes in diagnosis have resulted in unnecessary amputations.

FIG. 3. FIG. 4.

FIG. 3. Case 2. Aneurysmal bone cyst of tibia. Note the typical blown-out appearance.

FIG. 4. Case 2. Appearance 3 years following surgery. Note marked ossification within cyst.

PATHOLOGY

Grossly, when the surgeon removes the protective shell of bone he is confronted with a cystic cavity formed by large spaces containing fluid and nonstagnant blood which does not spurt nor pulsate but which wells up continuously until complete removal of the tissue is effected. Indeed, this constant welling-up of blood may be so severe as to prevent complete eradication, particularly of large lesions. The tissue encountered in the cavity is usually of meager amount and consists of a red or brownish mesh of fibrous tissue surrounding the blood-filled spaces which may measure several centimeters in diameter and are separated by this fibrous tissue containing osteoid or "fiber bone."

Microscopically, this fibrous tissue is seen to be formed of long, fusiform cells with elongated nuclei. In addition, hemosiderin-laden phagocytes and giant cells are observed at times almost lining the vascular spaces. This condition has been the greatest cause for confusion with true giant cell tumors. However, the main histologic differentiation is that in aneurysmal bone cyst the giant cells do not form a homogeneous pattern with regularly interspersed cells, and although multinucleated they seldom attain as large a size as in true giant cell tumors. In addition, the latter lacks the characteristic blood-filled, dilated vascular spaces. These are tortuous, large, and separated by fibrous stroma which contains no muscular layers, thus differentiating this lesion from true blood vessel tumors of bone.

Aspiration biopsy is useful because if large amounts of blood and scattered giant cells are obtained, such findings are strongly suggestive and, taken with the roentgenographic appearance, may be sufficient to permit a presumptive diagnosis of aneurysmal bone cyst.

TREATMENT

Treatment is predominantly surgical and is aimed at exposure and eradication of the entire lesion by thorough curettement supplemented by bone graft in the form of bone chips from bank bone or autogenous bone, when the cavity is large enough to require

FIG. 5. Case 5. Note destructive lytic lesion in ascending ramus of pubis. The typical eccentric blown-out appearance is lacking here.

it. When the lesion is located in the spine or in an area where surgical intervention is not feasible, roentgen therapy has proved of benefit and in some cases has produced a permanently satisfactory result.

Of our series, 13 were treated by surgery alone, 4 by roentgen therapy alone, 2 by a combination of these two methods, and 1 by radium implantation.

While the literature contains several reports of "spontaneous cure" of aneurysmal bone cyst, these are regarded as misleading since they have not been substantiated by sufficient clinical, roentgenographic, or microscopic evidence. Typical of this fact are 2 cases related by Lichtenstein that resulted in amputation. In one, the patient neglected treatment for 1 year after the diagnosis had been established by biopsy. By that time, the lesion which originated in the lower end of the humerus had destroyed the elbow joint together with the articular surfaces and corresponding segments of humerus, radius, and ulna. There was extensive damage to soft tissues with ulceration through the skin. Destruction had extended beyond the limits of repair and an upper extremity was lost by neglect of a "benign" lesion. The second case occurred in a man who deferred seeking medical advice for 5 years by the end of which time the condition, which originated in the lower portion of the tibia, had destroyed the lower ends of the tibia and fibula, all of the tarsal bones, and the proximal two-thirds of the metatarsals. It was associated with a bulky mass, soft tissue damage, and skin ulceration; here also an amputation was necessary.

No instances of unquestioned spontaneous healing in untreated cases have been observed by the authors. Surgical eradication by thorough curettage with or without bone grafting is undoubtedly the procedure of choice, particularly for accessible lesions. Roentgen therapy should be reserved for those that are considered surgically inaccessible.

CASE REPORTS

CASE 1. D. M., a 12 year old white male, injured his left thigh 5 weeks prior to admission. This was followed by pain, ecchymosis, and impairment of function for 2 weeks. Physical examination revealed a body configuration mildly suggestive of Frölich's syndrome with hypoplastic genitalia. The left leg presented marked swelling at the junction of the middle with the lower third of the thigh. The mass was tender to palpation, smooth in contour, and did not pulsate. The overlying tissues were moderately edematous, and some limitation of flexion of the leg upon the thigh was present. X-ray films disclosed a lesion arising from the midshaft of the femur with destruction of the cortex posteriorly, apparently not medullary in origin. It was surrounded by a thin shell of bone (Fig. 1).

Curettage and cauterization with zinc chloride was carried out on May 11, 1939. A large, soft, friable tumor mass was found in proximity to a sizable lytic defect on the midfemur. The lesion was extremely vascular. Pathologic diagnosis was aneurysmal giant cell tumor of a benign type. The patient made an uneventful recovery and was discharged on the thirteenth postoperative day; but he had to be readmitted 2 months later because of increase in the size of the bone lesion with further extension into the soft tissue as disclosed by x-ray films. He then received radiation therapy; a 1,600 roentgen tumor dose to the center of the lesion was delivered, factors 250 kilovolts, 1.5 centimeter copper filter, target skin distance 50 centimeters through a lateral port 18 by 12 centimeters and a 15 by 12 centimeter medial one. This treatment resulted in complete arrest of the disease, and satisfactory ossification of the lesion was noted on films taken 5 months later. There is still x-ray

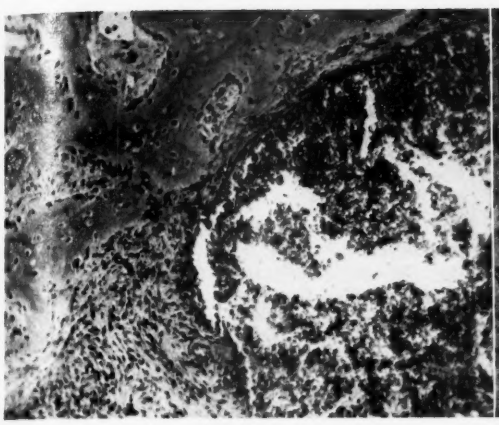
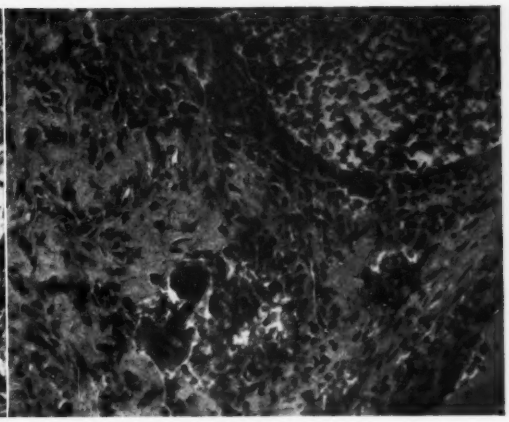


FIG. 6.



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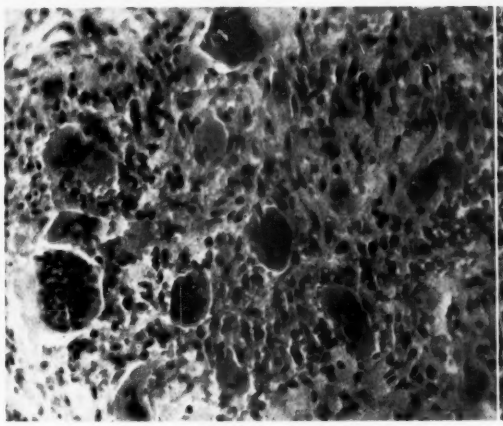

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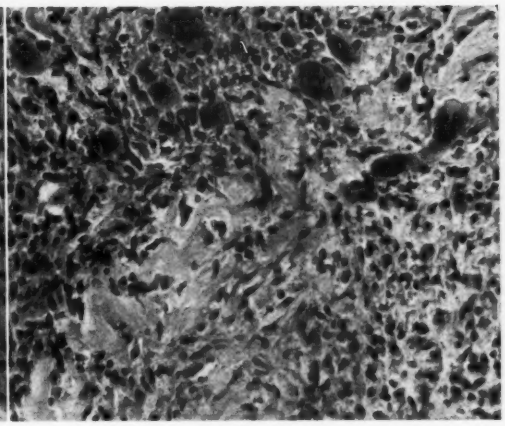

FIG. 9.

FIG. 6. Case 5. Illustrates the characteristic dilated, engorged vascular space abutting here on newly formed subperiosteal bone, the cortex having been eroded by the expanding lesion. The vascular space is lined by endothelial-like cells, and lacks a fibromuscular or elastic wall. Viable red cells are seen within the lumen; thrombosis is seldom seen. Hematoxylin and eosin, ×62.

FIG. 7. Case 5. Illustrates the endothelial-like cells lining the vascular spaces. They vary from spindle-shaped to cuboidal. Occasional giant cells are seen abutting on the vascular spaces. The adjacent supporting connective tissue stroma shows hemorrhagic suffusion, multinucleated giant cells, and osteoid formation. Hematoxylin and eosin, ×161.

FIG. 8. Case 5. Illustrates an area of supporting tissue in which the fibrous tissue is moderately cellular and where large numbers of multinucleated giant cells are present. It is areas such as this which might lead to an erroneous diagnosis of giant cell tumor. In the average case the major portion of the supporting connective tissue is a more adult type of fibrous tissue. Hematoxylin and eosin, ×161.

FIG. 9. Case 5. Illustrates, in addition to a giant cell area, osteoid formation. When osteoid formation is excessive and the connective tissue unusually cellular the lesion has been confused with osteosarcoma. Calcification of the osteoid was present in other areas. Hematoxylin and eosin, ×161.

evidence of this ossified lesion on the right femur (Fig. 2), but the patient has remained essentially asymptomatic and he was able to serve his term in the Navy. Review of the slides of the original lesion revealed that it was an aneurysmal bone cyst. Physical examination on September 21, 1955, more than 16 years after treatment showed a very satisfactory, sustained arrest of the lesion.

CASE 2. H. G., a 22 year old white male, gave a history of "twisting" his leg at work 6 months prior to admission, resulting in constant, moderate discomfort until a few weeks prior to admission, when he

started to limp and was conscious of a swelling in the left knee area. Physical examination showed a mass on the left tibia, impinging slightly upon flexion of the knee joint and causing a sense of fullness of the popliteal space. X-ray films disclosed a 6 by 4 centimeter, lytic, trabeculated lesion of the upper tibia associated with a bulging soft tissue mass protruding posteriorly and rimmed by a periosteal bone shell (Fig. 3).

On May 7, 1931, the patient underwent curettage and cauterization with zinc chloride. This treatment was followed by an uneventful recovery. While at that time the lesion was reported to be a benign giant cell tumor, review of the sections in the course of this study revealed it to be an aneurysmal bone cyst. The patient has remained essentially asymptomatic for over 24 years in spite of having sustained severe trauma to the affected area on 3 occasions (Fig. 4).

Case 3. C. R., a 9 year old white male, was admitted with a history of painless swelling of the left ankle over a period of 3 months. There was no record of trauma. Physical examination revealed a hard mass overlying the os calcis. X-ray films disclosed an expanded, lytic lesion of this bone destroying the superior cortex and associated with a soft tissue density mass. Aspiration biopsy yielded 50 cubic centimeters of blood. Following curettage and implantation of bone chips on April 1, 1954, the patient made an uneventful recovery and has remained asymptomatic to date. Pathologic diagnosis of the specimen was aneurysmal bone cyst and recent review of the sections has corroborated it.

Case 4. C. O., a 35 year old white male, complained of pain in the lower right thigh for 1 year. This became worse 3 months prior to admission when he "twisted" his leg. X-ray films showed an osteolytic lesion of the midshaft of the right femur measuring 6 by 4 centimeters and presenting loculation and expansion of the cortex. Following curettage on October 26, 1953 he made an uneventful recovery and has remained asymptomatic to date. Review of the sections has corroborated the original diagnosis of aneurysmal bone cyst.

Case 5. L. S., a 16 year old white female, had noticed pain over the right pubis for 4 months prior to admission, especially when walking, dancing, or exercising. This condition was associated with a "popping noise" in this area. No history of previous trauma was elicited. Physical examination was essentially negative except for moderate tenderness to pressure over the right pubis. X-ray films disclosed a 7 centimeter lytic lesion of the superior ramus destroying both medullary and cortical bone and presenting expansion and periosteal proliferation (Fig. 5). Aspiration biopsy specimen was reported as blood and a few giant cells. Following curettage on October 27, 1954, the patient made an uneventful recovery and except for moderate discomfort from a fracture at the operative site which remained undetected for 3 months, she has been asymptomatic. Both the original pathologic report as well as the recent review show that the lesion was an aneurysmal bone cyst (Figs. 6, 7, 8, and 9).

Case 6. C. L., a 16 year old white female, complained of backache 5 months prior to admission. Three months later she discovered a mass in the lumbar area. There was no history of previous injury. She underwent a negative exploratory laparotomy, and an open biopsy of the spinal lesion elsewhere. Submitted films revealed extensive destruction of the body of the second lumbar vertebra, associated with a large soft tissue mass protruding eccentrically into the adjacent tissues and surrounded by a thin shell of cortical expansion (Fig. 10). The submitted sections were reviewed and the pathologic diagnosis was aneurysmal bone cyst. Because of the location of the lesion it was deemed advisable to institute radiation therapy, and the patient received a total tumor dose of 2,000 roentgens over a 9 day period. She was placed in a Taylor brace and immediate amelioration of symptoms follow. The draining sinus that had been present since her biopsy elsewhere healed and she has remained asymptomatic to date, 13 months after treatment. Recent films show complete arrest and ossification of the lesion (Fig. 11). Review of the sections has corroborated the original diagnosis.

Case 7. P. G., a 14 year old white female, fell in June of 1943 and felt a "sprain" of her left thigh. Following unsuccessful conservative measures, an x-ray film was taken which disclosed a large, osteolytic lesion of the right pubis and acetabulum. The patient was referred to Memorial Center, in January 1944, where an extensive curettage was carried out on February 2, 1944. She made an uneventful recovery and has remained asymptomatic to date. X-ray films show complete arrest and good calcification and bone regeneration. Original pathologic diagnosis was bone cyst but review of the same sections disclosed an aneurysmal bone cyst.

Case 8. S. B., a 16 year old white male, was admitted with a history of pain in the right leg for 6 months and swelling of 2 months' duration. X-ray films showed a large, lytic lesion of the right tibia without trabeculation and entirely surrounded by a shell of cortical bone having a blown-out pattern. Aspiration biopsy yielded 30 cubic centimeters of blood; this procedure was repeated and specimen reported as blood and giant cells. Curettage and grafting were carried out on May 1, 1937. The patient made an uneventful recovery and has remained asymptomatic for over 18 years. He was able to serve in the Navy for a period of 6 years after his operation. The original pathologic diagnosis was fibrosing, ossifying giant cell tumor but review of these sections has proved it to be an aneurysmal bone cyst.

Case 9. A. A., a 13 year old white female, gave a history of low back pain of 3 months' duration, noticed

particularly on bending down or when lying flat on her back. Physical examination demonstrated tenderness over the sacrum, and rectal palpation revealed a large mass on the anterior surface of this bone. X-ray films disclosed a 5 centimeter lytic lesion of the lower sacrum associated with a denser-than-water globular shadow. Curettage and autogenous grafting from her own right ilium were performed on December 18, 1947. She made an uneventful recovery but after 3 months had to be readmitted for increase in the size of the lesion. Again curettage was carried out and the cavity was filled with bone chips from the bank. A good result with calcification ensued and the patient has been asymptomatic to date, 7½ years after her second operation. The original pathologic report was "bone cyst with giant cell reaction in the wall"; but review of the sections proved that the lesion was an aneurysmal bone cyst.

CASE 10. M. M., a 26 year old female, gave a history of pain and tenderness over the right groin and perineum of 3 weeks' duration. There was no history of previous trauma and pain was aggravated by pressure or weight-bearing. Physical examination revealed enlargement of the descending ramus of the right pubis, and x-ray films disclosed a large, expansile, multilocular, lytic lesion of the right pubis, suggestive of a giant cell tumor. Aspiration biopsy report read: "Smear shows rare cells of type seen in giant cell tumors, but this may go with any destructive lesion of bone." The patient then received a total tumor dose of 1,200 roentgens in October of 1936; and because of recurrence of symptoms and increase in size of the lesion, in December, 1940, she was given an additional course of roentgen therapy consisting of a total tumor dose of 1,120 roentgens. A good result was obtained; she has remained asymptomatic to date, 15 years after her second course of roentgen therapy. X-ray films show good calcification and bone regeneration. A review of the pathologic material has permitted us to include this case in the present series.

CASE 11. A 14 year old white female complained of functional disability of her back for 1 year prior to admission. Original x-ray films showed no abnormality except a mild degree of lordosis. There was no history of trauma. Four months prior to admission she developed a severe pain in the lumbar region of sciatic type radiating to her posterior left thigh and leg. Two weeks prior to admission x-ray films demonstrated a tumor of the spine. After a biopsy, performed elsewhere, was reported as "bone angioma," the patient was admitted to Memorial Hospital. She was placed in a body cast and, since a review of the sections confirmed the diagnosis of bone angioma, roentgen therapy was begun. She received 1,000 roentgens (air), 250 kilovolts, 1.5 centimeter copper filter, target skin distance 50 centimeters from October 30 to November 4, 1940; and from December 31, 1940 to January 3, 1941, an additional air dose of 900

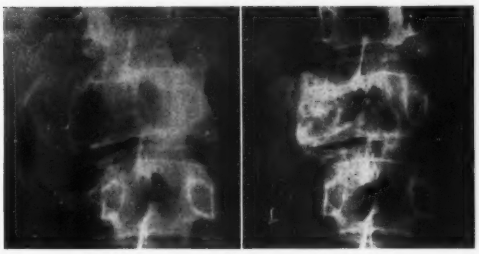

FIG. 10. FIG. 11.

FIG. 10. Case 6. Aneurysmal bone cyst of vertebra. Note the blown-out appearance beyond the normal confines of the vertebral body.

FIG. 11. Case 6. Appearance 1 year following treatment. Note the repair that has taken place in this period of time.

roentgens was administered with the same factors except for a target skin distance of 70 centimeters. She remained in the body cast for several months because of a pathologic fracture of the body of the fourth lumbar vertebra, but gradually all her symptoms subsided and calcification of the bulky, large lesion of the lumbar vertebrae was demonstrated in subsequent films. She was fitted with corrective braces for her scoliosis and has remained well and asymptomatic, except for an occasional sensation of "pins and needles" on the posterior aspect of her left thigh and leg. No atrophy of bones or muscles has followed the treatment. A review of the original sections proved the lesion to be an aneurysmal bone cyst.

CASE 12. Y. R., a 13 year old white female, (Fig. 12) was admitted with a history of pain in the right hip over a period of 3 or 4 months that was aggravated by walking or direct pressure. X-ray films demonstrated a trabeculated, lytic lesion of the right acetabulum (Fig. 13) and were reported as highly suggestive of a malignant bone tumor. Aspiration biopsy specimen was reported as "blood and epulis type of giant cells" and although biopsy was repeated twice under fluoroscopic control no further information was obtained. On April 29, 1948 an open biopsy and curettage of a brownish, bloody, meshy lesion were carried out. The microscopic report was: "inadequate for diagnosis of a malignant tumor; irregular bone trabeculation and an area of giant cells; the lesion mostly suggestive of bone cyst." The patient made an uneventful recovery, and the symptoms diminished considerably. However, follow-up films 4 months later disclosed a marked increase in the size of the lesion, and the radiologist feared the possibility of an osteogenic sarcoma. Another aspiration biopsy was performed; this was reported: "blood and occasional pigment laden macrophages, no tumor cells." On September 16, 1948, a second operation was performed which revealed a multiloculated cystic cavity with tissue varying from dark yellow to

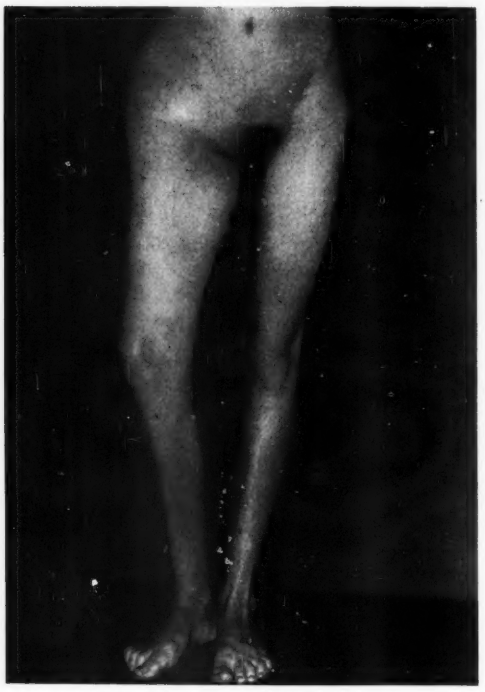

FIG. 12. Case 12. Aneurysmal bone cyst of ilium. Appearance of patient on admission.

brown in color. The hemorrhage was quite profuse and the patient received 1,500 cubic centimeters of whole blood during the procedure. The final paraffin sections were reported as "multiloculated, hemorrhagic bone cyst." This patient had a moderately complicated recovery with fever that lasted for 3 months postoperatively which was attributed to hemorrhage within the lesion itself and to urinary tract infection. This condition cleared up under antibiotic therapy, and except for the presence of a huge mass (Fig. 14) which x-ray films show to be well calcified now, she has remained symptom-free for 7 years and is healthy and active. Review of the pathologic material has confirmed the diagnosis of aneurysmal bone cyst.

CASE 13. T. R. a 35 year old white priest, was admitted with a history of moderate pain on abduction of the right shoulder of 6 weeks' duration. No history of trauma was elicited. X-ray films disclosed a trabeculated, lytic lesion overlying the deltoid tuberosity, measuring 1½ inches in diameter and interpreted as suggestive of chondroblastoma or a giant cell tumor. On April 7, 1954 the lesion was curetted and the patient made an excellent recovery. There is evidence of adequate calcification and bone regeneration 10 months after operation. The original pathologic diagnosis was aneurysmal bone cyst versus giant cell tumor. A final pathologic diagnosis of aneurysmal bone cyst was made after review of the microscopic sections.

CASE 14. S. H., a 10 year old white female, had noticed a moderately tender mass below the right knee 10 days prior to her admission. It was associated with temperature elevation and caused her to limp. X-ray films taken elsewhere revealed what was thought to be a juvenile cyst of the upper right tibia and she was referred to Memorial Center for treatment. On physical examination a nonpulsating, moderately tender mass, measuring 6 by 4 centimeters, was noted. The submitted films disclosed a slightly trabeculated, lytic lesion 8 centimeters in diameter, causing moderate expansion of the periosteum anteriorly and laterally. Aspiration biopsy yielded a large amount of fresh blood only. At operation, a typical aneurysmal bone cyst was encountered. The lesion was curetted thoroughly and chips of homologous bone were used to fill the cavity. The patient made an uneventful recovery and was discharged on the thirteenth postoperative day. Both the original pathologic report and the review of the material in connection with this study corroborated a diagnosis of aneurysmal bone cyst.

CASE 15. H. S., a 17 year old white female, gave a history of moderate pain in the region of the fourth metatarsal bone of the left foot of 4 or 5 months' duration, aggravated by weight-bearing and activity. Three weeks prior to admission to Memorial Hospital this tumor was curetted at another hospital. It was described by the referring surgeon as a cystic cavity containing dark brown, hemorrhagic tissue. The microscopic sections and x-ray films were reviewed at Memorial Hospital and a diagnosis of benign giant cell tumor was made in August 1937. The patient was followed carefully and x-ray films taken in February 1938 demonstrated definite recurrence and activity associated with pain and tenderness to palpation. She was readmitted and on March 22, 1938 a resection of the distal three-fourths of the left fourth metatarsal bone was carried out. The patient made an uneventful recovery and has remained symptom-free to date, more than 17 years after her second operation. A review of the microscopic sections of this case has established a diagnosis of aneurysmal bone cyst.

CASE 16. D. P., a 23 year old white male, was referred to Memorial Hospital in March 1954, with a chief complaint of pain in the right lower abdominal quandrant of 3 or 4 months' duration. X-ray films taken elsewhere showed a lytic lesion of the right ilium measuring 6 by 3 centimeters in diameter. As this patient had an episode of hematuria in 1950, intravenous urograms had been taken at that time. Comparison of these films showed that the lesion of the iliac bone had been present since then and the only interval changes were a moderate increase in size of the lytic process and the appearance of a central area of trabeculation. The right kidney collecting

FIG. 13.

FIG. 14.

FIG. 13. Case 12. Roentgenographic appearance of lesion before treatment.
FIG. 14. Case 12. Appearance 6 years later following surgery.

system showed a congenital type of mild bifid pelvis which was also present in the left kidney to a lesser degree; but neither side presented appreciable changes in the 4 year interval.

The bone lesion was diagnosed as suggestive of a benign tumor, fibrous dysplasia, angioma or cartilage lesion being favored by our x-ray department.

On March 22, 1954 a segmental resection of the lesion-bearing portion of the right iliac bone was done. The patient made an uneventful recovery and has remained symptom-free to date. The original pathologic diagnosis was aneurysmal bone cyst and recent review of the sections has corroborated it.

CASE 17. M. M., a 26 year old white female, gave a history of moderate pain in the right shoulder of 6 months' duration, and particularly aggravated by lying down on this side. The pain increased in severity within a few months and a swelling of the distal end of the right clavicle appeared 2 months prior to her admission. X-ray films showed an expansile, lytic lesion of the right clavicle with loss of the cortical outline along the superior border and associated with a soft tissue mass projecting superiorly into the adjacent tissues. An aspiration biopsy was performed and it was reported to show many giant cells of the epulis type suggestive of a benign giant cell tumor. From July 5 to 15, 1944, the patient underwent radiation therapy and received a total tumor dose of approximately 1,208 roentgens, factors 250 kilovolts, 1.5 centimeter copper filter, target skin distance 50 centimeters through a 14 by 7 centimeter portal. There was marked regression of the lesion and calcification was evident on the films taken 3 months later. This patient has remained asymptomatic to date, more than 11 years after her treatment. The skin overlying the lesion of the clavicle shows no evidence of radiation damage and there has been adequate bone regeneration.

CASE 18. J. K., a 35 year old white male, had discovered a hard mass, the size of a walnut, in his left groin 6 months prior to his admission. Two months later he felt severe pain radiating down the anterior aspect of his left thigh which was particularly aggravated by walking or working. The pain increased in severity and the mass continued to grow. Physical examination on admission (1923) revealed a hard, ovoid, nonpulsating mass apparently attached to the left pubis and measuring 5 by 7 centimeters. X-ray films demonstrated a lytic lesion of the left pubis having a blown-out slightly trabeculated pattern. On July 2, 1923, under local anesthesia, an open biopsy was performed and bare tubes of radium were inserted into the lesion. The operative wound was closed without drainage, and the patient made an uneventful recovery. Three months later there was gross clinical evidence of regression of the lesion, and x-ray films showed calcification taking place as well. He has remained asymptomatic for a period of more than 32 years, and recent films disclose adequate reossification of the lesion. The skin overlying the left pubis shows moderate telangiectasis from the original radium therapy, but otherwise the result is satisfactory. A review of the sections diagnosed as giant cell tumor in 1923 has proved the lesion to be an aneurysmal bone cyst. This case constitutes our longest follow-up in the present series.

CASE 19. J. G., a 21 year old white female, was admitted to Memorial Hospital on May 22, 1936 with a history of sprain of the left ankle 1 year previously. Since then patient had had recurrent epi-

TABLE I.—SUMMARY OF CASES OF ANEURYSMAL BONE CYST

Case No.	*Name*	*Age, yrs.*	*Sex*	*Location*	*History of trauma and type*	*Method of treatment*	*Result*
1	D.M.	12	M	Femur	Yes, fall (no fracture)	Curettage + radiation, 1,600 r. T. D.	Cured, 16 years
2	H.G.	22	M	Tibia	Yes, twist	Curettage	Cured, 24 years
3	C.R.	9	M	Os calcis	No	Curettage	Cured, 19 months
4	C.O.	35	M	Femur	No	Curettage	Cured, 2 years
5	L.S.	16	F	Pubis	No	Curettage	Cured, 1 year
6	C.L.	16	F	L-2	No	Radiation, 2,000 r. T.D.	Cured
7	P.G.	14	F	Pubis	Yes, fall	Curettage	Cured, 11 years
8	S.B.	16	M	Tibia	No	Curettage	Cured, 18 years
9	A.A.	13	F	Sacrum	No	2 curettages 3 mos. apart	Cured, 7.5 years
10	M.M.	26	F	Pubis	No	Radiation, 1,200 r. Oct. '36; 1,120 r. Dec. '40	Cured, 15 years
11	M.A.	14	F	L-2	No	Radiation, 1,305 r.	Cured, 15 years
12	Y.R.	13	F	Ilium	No	2 curettages 4 months apart	Cured, 7 years
13	T.R.	35	M	Humerus	No	Curettage	Cured, 19 months
14	S.H.	10	F	Tibia	No	Curettage	Cured, 4 months
15	H.S.	17	F	Metatarsal	No	Curettage fol. by segmental res. in 9 months	Cured, 17 years
16	D.P.	23	M	Ilium	No	Segmental resection	Cured, 20 months
17	M.M.	26	F	Clavicle	No	Radiation, 1,208 r. T.D.	Cured, 11 years
18	J.K.	35	M	Pubis	No	Radium tubes	Cured, 32 years
19	J.G.	21	F	Fibula	Yes, sprain	500 r., followed by curettage in 2 months	Cured, 19 years
20	G.L.	44	M	Radius	No	Curettage	Cured, 1 year

sodes of pain over the lateral aspect of the lower leg. She had noticed progressive swelling of this area for 2 months prior to admission. X-ray films disclosed an expansile, trabeculated lesion of the lower end of the left fibula. An open biopsy was performed elsewhere, and the sections were interpreted as benign giant cell tumor (here as well as by other pathologists). On June 10, 1936, 500 roentgens (in air) were delivered to the lower left leg through a 7 centimeter cone; other factors were not stated. Because of the x-ray appearance, she was readmitted and on August 20, 1936, a curettage of the lesion followed by cauterization of the cystic cavity was carried out. The patient made an uneventful recovery and was discharged on the thirteenth postoperative day. The pathologic diagnosis on the specimen was: sclerosing type of giant cell tumor. She has remained asymptomatic for more than 19 years following her operation. There is roentgenologic evidence of adequate recalcification and bone regeneration. A recent review of the microscopic sections has proved that this lesion was an aneurysmal bone cyst.

CASE 20. C. L., a 44 year old white male, first noticed a dull ache in his left wrist in May, 1954. One month later a swelling developed in this area associated with pain on pressure and motion; this condition progressively increased. Roentgenograms taken elsewhere showed what was believed to be a giant cell tumor. Physical examination on admission to Memorial Hospital was essentially negative with the exception of a fusiform swelling of the distal end of the left radius. Submitted films disclosed an expansile, lytic, trabeculated lesion, measuring 4 centimeters and having a peculiar blown-out pattern. An aspiration biopsy was carried out under local procaine infiltration and benign giant cell tumor was reported. On September 23, 1954, a curettage and homologous bone graft was carried out, and the patient made an uneventful recovery. He has remained symptom-free for over a year and there is adequate calcification and bone regeneration present as revealed in his follow-up films. A microscopic diagnosis of aneurysmal bone cyst has also been established based on a study of the material obtained at operation.

SUMMARY

The literature on aneurysmal bone cyst has been reviewed and the characteristic clinical, roentgenologic, and microscopic features of the lesion have been presented. Emphasis has been laid on some aspects of treatment. Twenty cases from the Bone Tumor Department of the Memorial Center for Cancer and Allied Diseases have been reported.

CONCLUSIONS

Aneurysmal bone cyst is a well defined lesion of unknown etiology and relatively benign course. There is sufficient evidence to support the theory that it may not be a true neoplasm, and that it is definitely not a traumatically induced hematoma. The lesion is often mistaken for giant cell tumor, and less frequently for juvenile bone cyst or bone angioma. The main practical consideration is to distinguish it from the telangiectatic type of osteogenic sarcoma and thus avoid unnecessary amputation. The treatment of choice is: surgical eradication by curettage complemented by bone graft whenever necessary. Roentgen therapy should be reserved for surgically inaccessible lesions. Delay in treatment may result in severe damage to bones, joints, and soft parts and may eventually necessitate amputation. The authors have not observed any cases of spontaneous regression and there are no well documented examples of it in literature.

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RESIDUAL STONE IN THE BILIARY DUCTS

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CHOLEDOCHOTOMY for the removal of stone from the comon bile duct was first performed only 67 years ago. Since that time this operation has become a common operative procedure and, with increasing use and the addition of refinements, is gradually becoming more reliable and efficient. The method is still far from perfect, however. Common duct exploration, carried out as it is in 20 to 40 per cent of operations for stone in the biliary system, results in the finding of stones in 25 to 50 per cent of the ducts opened. Residual or overlooked stones are reported to remain in 10 to 25 per cent of all common ducts explored.

At the Vancouver General Hospital from 1949 to 1954, 745 cholecystectomies and 106 primary common duct explorations were carried out. Stones were found in 45 of these common duct explorations, an incidence of only 14 per cent common duct explorations of which 41 per cent were positive. During the same period there were an additional 34 postcholecystectomy or secondary common duct explorations in which residual stones were found. In 12 of these cases, the primary surgery was carried out at the Vancouver General Hospital between 1949 and 1954, during which time 106 primary common duct explorations were performed. Therefore, the incidence of residual or missed stone in common duct exploration at the Vancouver General Hospital between 1949 and 1954 was approximately 11 per cent. With a longer follow-up period, this figure would be appreciably higher.

The operative mortality of primary common duct exploration may be very low but in the hands of the average surgeon is 4 to 10 per cent. This figure increases for patients over 50 years of age and for secondary exploration for residual stone. At the Vancouver General Hospital, there were 3 deaths in 34 secondary common duct explorations, a mortality of approximately 9 per cent (Others have reported a much higher mortality.) It is apparent, therefore, that postoperative residual stone in the biliary ducts is a very common and serious problem in present day biliary surgery.

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CLINICAL MATERIAL

In the records of the Vancouver General and Shaughnessy Military Hospitals, there are 39 cases of postcholecystectomy or residual stone in the biliary ducts proved by reoperation or autopsy between 1949 and 1954. In approximately two-thirds of all the cases, the original cholecystectomies were carried out several years ago, and often in other hospitals. In many, there is no way of knowing whether the common duct was explored at the first operation. These 39 cases have been studied in an attempt to determine the clinical characteristics of residual stone in the biliary ducts and how the incidence may be reduced.

There were 25 females with a peak incidence at 55 years of age and 14 males with a maximum incidence at 70 years of age.

The cases fell into two distinct categories: group 1—28 cases in which the diagnosis was not made during the immediate postoperative and hospitalization period of the initial operative procedure; group 2—11 cases in which early postoperative diagnosis was accomplished.

Group 1. The diagnosis of residual stone was stimulated in all of the group 1 cases by the recurrence of pain after cholecystectomy. This pain recurred during the first year in 50 per cent of the cases. In the other 50 per cent, the pain recurred at various times up to 25 years postcholecystectomy.

FIG 1. Cholografin showing 3 residual stones.

FIG. 2. Cholografin showing 1 residual stone.

When the nature of the recurrent pain was recorded, it was always upper abdominal, usually epigastric, and often in the right upper quadrant. Occasionally, the pain involved the whole upper abdomen and it radiated to the back in the majority of cases. Many patients were unable to distinguish the pain from that experienced before cholecystectomy. Attacks of pain lasting from a few hours to a few days, usually severe, and associated with anorexia, nausea, or vomiting were usual. These attacks tended to increase in severity and frequency with time, occurring almost daily in some cases and only every few months in others. Approximately one-third of the patients suffered the pain for 1 year, one-third for 2 to 5 years, and one-third for 6 to 25 years before the residual stone was removed.

Jaundice was present on admission or had occurred since the onset of recurrent pain in 20 of the 28 cases. This condition was severe in 5, moderate in 4, and slight in 11 cases. Severe jaundice was uncommon therefore, while no jaundice appeared in nearly one-half of the cases. Pruritus was present in the severe cases only. When present, the jaundice was fluctuant, appearing just after the onset of attacks of pain and associated with light stools and dark urine. In 9 of the 20 jaundiced patients, chills and fever were reported with the attacks, while this occurrence was rare in the absence of jaundice. In all patients, jaundiced or otherwise, serum protein, thymol turbidity, and cephalin flocculation liver function tests were normal. Alkaline phosphatase was elevated in the jaundiced patients but not markedly so, being 10 to 40 King-Armstrong units in the majority of cases and never higher than 60 King-Armstrong units. The prothrombin time was always decreased in the presence of jaundice but in only 2 patients was it below 50 per cent of normal. Weight loss was rarely present even in the long term cases; however, in the 2 exceptions it was 15 and 35 pounds.

In the majority of the 28 cases in group 1, the diagnosis was made on the basis of the clinical characteristics alone. There were 6 cases in which the clinical diagnosis was confirmed by means of intravenous cholangiography with cholografin. This technique reveals the biliary ducts in a high percentage of cases, particularly in the absence of the gallbladder, jaundice, or liver disease. This new technique greatly facilitates the diagnosis of residual common duct stone.

Group 2. The 11 cases in group 2 are of even greater interest. The diagnosis was made in 9 of these 11 cases by postoperative cholangiography through the T tube. In 8 cases, the diagnosis was confirmed at operation and in 1 patient, in whom an unsuccessful re-exploration through the duodenum caused shock and death, the stone was

FIG. 3.

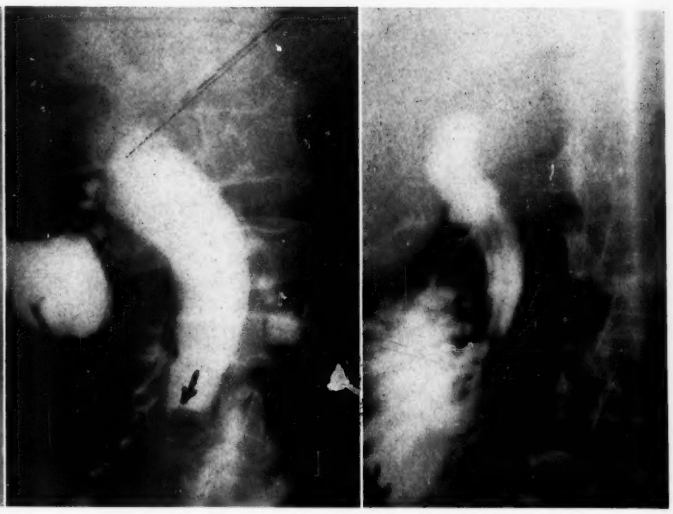

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FIG. 4.

FIG. 3. Postoperative cholangiogram showing residual ampullary stone.
FIG. 4. a, Residual large ampullary stone is shown; b, a few days after removal duct system has returned to normal size.

found at postmortem examination. The other 2 patients died soon after cholecystectomy, and in each a residual common duct stone was found at autopsy. That the postoperative cholangiogram findings were confirmed at operation or postmortem examination in all 9 cases so diagnosed is a great tribute to the value of this method. Postoperative T-tube cholangiography has been accepted as standard procedure following choledochotomy and, as these cases show, is of value. It must be done in such a way as to eliminate any possibility of confusing air bubbles. The common practice of irrigating with saline prior to injection is unnecessary and apt to introduce bubbles. Instead, the T tube should be allowed to fill spontaneously with bile then diodrast should be injected directly. A residual ampullary stone is well shown by postoperative cholangiogram (Fig. 3).

Figure 4a is a cholangiogram obtained by injecting a persisting postoperative biliary fistula and shows a large ampullary stone. The postoperative cholangiogram (Fig. 4b) taken a few days after re-exploration demonstrates the rapid return of the duct system to normal size after removal of the stone. This rapid decrease in size of the common duct after successful decompression is particularly well shown in many of these cases and is so marked as to suggest that any enlarged common duct must have been recently obstructed.

OPERATIVE CHOLANGIOGRAPHY

It follows that if postoperative injection roentgenograms of the biliary ducts are valuable in the diagnosis of residual common duct stone, then injection roentgenograms taken while the operation is in progress should help to prevent leaving a residual common duct stone. A recent survey by Clark of leading hospitals and surgeons revealed that operative cholangiography is being carried out in 75 per cent of these hospitals and by 66 per cent of the surgeons.

Diagnostic operative cholangiography. Operative cholangiography consists of two distinct types. First is the diagnostic or predissection

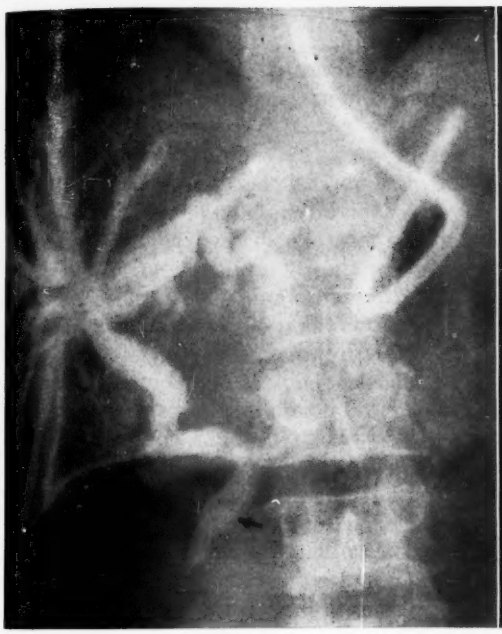

FIG. 5.

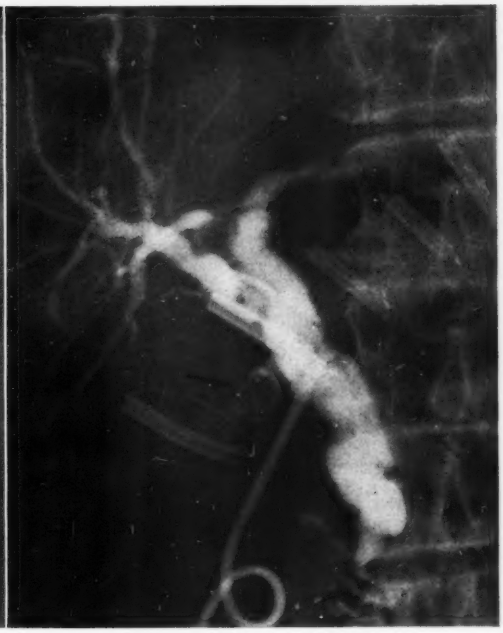

FIG. 6.

FIG. 5. Control operative cholangiogram showing residual stone near ampulla.
FIG. 6. Control operative cholangiogram showing stone in cystic duct stump not found at re-exploration.

operative cholangiogram used to visualize the common duct whenever there is no clear clinical or operative indication for exploration. In 1954, Mehn stated that since 1950 he had done operative cholangiograms 113 times under these circumstances and in 10 cases had found an unsuspected stone. We have had similar experiences at Shaughnessy Hospital. Because of experiences such as this, most surgeons adept at operative cholangiography do them in all cases in which there is any doubt as to the need for choledochotomy. Hicken, who has done a large series of cholangiograms of all types stated that operative cholangiography shortened many operations because it eliminated unnecessary exploration of the common duct. Mixter reported that by using operative cholangiography he had been able to reduce the incidence of common duct exploration by 14 per cent and to increase the frequency of positive explorations.

The success of diagnostic operative cholangiography depends upon the use of a meticulous technique. A few of the important details are as follows: A plate holder either built into the operating table or under the mattress and a suitable grid are advisable. However, thin patients can be treated without a grid with good results. The cystic duct is immediately exposed and ligated near the gallbladder. The cystic duct is opened near the common duct, and a No. 18 polythene tube or a No. 8 urethral catheter, previously filled with 35 per cent diodrast to prevent any possible injection of air bubbles, is introduced for ½ inch and tied in place. A 20 cubic centimeter syringe containing 35 per cent diodrast is connected to the tube and aspirated until bile fills the tubing. All instruments and towel clips are removed. Finally, 5 cubic centimeters of diodrast are injected slowly and the anesthetist stops the breathing while the picture is taken. The

TABLE I.—CONTROL OPERATIVE CHOLANGIOGRAPHY IN 6 CASES

Finding of cholangiogram	*Found at operation by—* *Further supraduodenal explorations*	*Duodenostomy*
1 stone at ampulla	—	+
1 stone at ampulla	—	+
1 stone at ampulla	—	+ and retrograde irrigation
4 stones lower end	+ (1 stone missed)	—
3 stones lower end	+	—
1 stone at ampulla	—	+

plates are changed and another picture is taken after 20 cubic centimeters are injected. The 5 cubic centimeter injection gives a light picture and shows small stones more clearly. While the picture is being developed, the gallbladder is removed. It is advisable to have a roentgenologist view the plates in the operating room, as they can be misread. Mehn stated that in none of his cases in which an operative cholangiogram was negative and the common duct not explored had stone been found later.

It is of particular interest that in 23 of these cases there was no history of common duct exploration at the time of the primary surgery. Probably, in many, the accepted indications for exploration of the duct were present and not recognized by the surgeon; in others, however, there may have been no definite indication. Surely, now that diagnostic operative cholangiography is an efficient technique, it should be carried out in any case of cholelithiasis before a final decision is made to omit common duct exploration. The incidence of both residual stone and unnecessary primary common duct exploration should be reduced by the adoption of this method whenever clear-cut clinical indications for common duct exploration are lacking.

TABLE II.—RESIDUAL STONES IN 39 CASES

	No. of cases
Dilatation of common duct	
None	1
Slight	3
Moderate	6
Marked	12
Not recorded	17
No. of residual stones found	
1	23
2	6
3	5
3+	5
Location of residual stones	
Hepatic ducts	4
Cystic duct	3
Proximal common duct	6
Distal common duct or ampulla	16
Not recorded	10

Control operative cholangiography. The second type of operative cholangiography may be called a control operative cholangiogram. It is done on the operating table through the T tube, after common duct exploration and before closing the wound, to detect a residual stone. Figure 5 is a reproduction of one of these control operative cholangiograms showing a residual stone near the ampulla.

In this series of 39 cases, control operative cholangiography actually revealed further residual stones in 10 cases at the conclusion of choledochotomy and resulted in their removal in 6. Table I shows the cholangiographic findings and how the further stones were found in the 6 cases. The value of duodenostomy under these circumstances is apparent.

In 4 cases the control operative cholangiogram was read as negative by the surgeon and no further search was made. Each of these 4 was read later by a roentgenologist as positive. Cholangiograms should be read in the operating room by a roentgenologist whenever possible. The great value of operative cholangiography is apparent, and no less apparent is the fact that supraduodenal palpation, irrigation, and probing constitute a very incomplete method of exploring the common duct.

CYSTIC DUCT STUMP

In this series, there were 5 residual cystic duct stumps, 3 of which contained stones. Gray and Sharpe of the Mayo Clinic reported on a series of 33 cystic duct stumps in 1944. Seven of these contained stones, and in all cases the patients were immediately relieved of their recurrent pain by excision of stump and stones. Of the remaining 26 patients without stones, only 65 per cent were relieved of their complaint by excision. Figure 6 is a control operative cholangiogram

showing a residual stone in a cystic duct stump that was not found at re-exploration of a common duct containing residual stones. This cholangiogram was read mistakenly as negative by the surgeon. The need for ligation of the cystic duct reasonably close to the common duct is obvious.

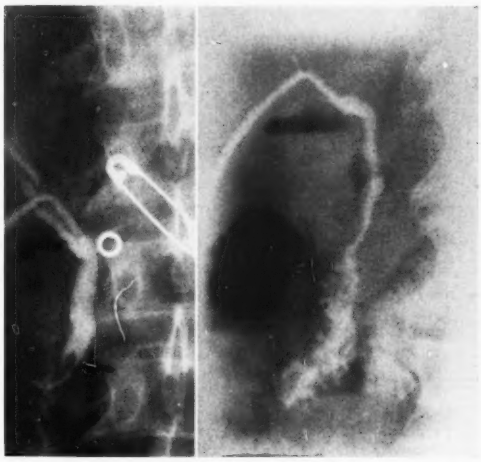

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FIG. 7. a, Ampullary stone present; b, final postoperative cholangiogram.

METHODS OF REMOVAL

Finally, we come to a discussion of methods for the removal of residual common duct stone. In this series of 39 patients, an attempt was made to remove the residual stones in 37 with success in 34 patients, 1 of whom died of a pulmonary embolus. Failure in the other 3 instances was due to the fact that: (1) Myriads of small stones were present in the hepatic radicals which kept repeatedly plugging first the T tube and later a partial stricture of the common duct. The patient died 3 months postoperatively of cholangitis with a persistent biliary fistula. No autopsy was obtained. (2) Residual stones were missed because only duodenostomy and retrograde exploration were performed. The patient died in shock in the immediate postoperative period and stone was found at postmortem. (3) Onset of shock during the course of operation (bile peritonitis present) forced early cessation before exploration was completed. The patient died 2 months postoperatively of suppurative cholangitis and stone was found at postmortem examination. The other 2 cases were diagnosed at autopsy, no secondary surgical procedures having been done.

The number and location of the residual stones and the degree of dilatation of the ducts in these 39 cases are summarized in Table II. Obviously, residual stones are often multiple and they may lie anywhere in the duct system. The need for complete exploration proximally and distally including the cystic duct stump is apparent.

Various combinations of the methods available were used to remove the stones in 34 of the cases in this series as outlined in Table III.

In 9 cases, purely mechanical supraduodenal exploration of the common duct failed to reveal the residual stones. Success was only achieved in these cases with the help of control operative cholangiography. In 2 cases, the stones were found by further supraduodenal exploration of the duct after cholangiography.

In 7 cases, duodenostomy following a negative supraduodenal choledochotomy resulted in the finding of a residual stone. In primary or secondary explorations of the common bile duct duodenotomy and retrograde exploration of the duct are indicated whenever there is any suspicion from supraduodenal exploration or cholangiography that any obstruction remains at the lower end of the common bile duct.

Ever since Pribram's article in 1935 on the nonoperative removal of stones by chemical irrigation of the T tube with ether, there has been a sustained argument as to the usefulness of this method. The objections to the

TABLE III.—METHODS USED TO REMOVE RESIDUAL STONES

	No. of cases
Choledochotomy	24
Choledochotomy plus control operative cholangiography	2
Choledochotomy plus duodenostomy	3
Choledochotomy plus control operative cholangiography and duodenostomy	4
Choledochotomy plus chemical irrigation T-tube	1

method are that it is often painful, only occasionally successful, and takes too long. Some fear that it may cause cholangitis. Behrend reports success in 6 of 20 cases using an alcohol and ether drip twice daily after 2 per cent procaine instillation. In this series, chemical solution was tried in 4 cases and succeeded once. In this case, an ampullary stone was demonstrated (Fig. 7a). The stone disappeared after 3 irrigations with 1/1500 nupercaine 10 cubic centimeters followed by alcohol and ether. The final postoperative cholangiogram (Fig. 7b) showed the stone removed and again the rapid decrease in duct size in a few days.

It seems that an occasional residual stone may be removed by irrigation of the T tube and that the method should be given a short trial when a stone is revealed by the postoperative cholangiogram. Certainly, there seems to be no justification for persisting with this method of treatment beyond a few days, however.

CONCLUSIONS

1. Postoperative or residual stone in the biliary ducts presents a common and important surgical problem.

2. Not infrequently, mechanical exploration of the common bile duct through a supraduodenal choledochotomy must be augmented by control operative cholangiography or duodenostomy or both if residual stones are to be found.

3. Residual common duct stone often results from failure to explore the duct at the primary operation. The incidence of residual stone and of unnecessary common duct exploration at the primary surgery should be reduced by the more frequent use of diagnostic operative cholangiography.

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THE EFFECT OF COMPRESSION ON THE GROWTH OF EPIPHYSEAL BONE

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IT WAS DEMONSTRATED BY HAAS (3) in 1945 that the longitudinal growth of bone in the distal femur and other epiphyses in dogs could be arrested by mechanical obstruction. In an attempt to stimulate the growth of long bones in the dog, Haas used wires of dissimilar metals to produce an electric current across the epiphyseal line. The wires were looped through the epiphysis and adjacent diaphysis, and as growth progressed a mechanical obstruction also developed that stopped the growth of bone. Haas (4, 5) has further stated that if mechanical obstruction is removed after growth has been arrested for a period of time, the epiphyseal plate is found to be viable and growth is again resumed, but the rate and amount of growth were not definitely established. Blount and associates (1, 2) have made extensive application of this principle in the arrest of bone growth in children for the purpose of equalizing leg lengths. In his extensive investigation Blount has stated that the force exerted by the growth of bone is relatively great and is sufficient to bend and eventually break 1 steel staple of $^{3}/_{32}$ inch in diameter on each side; if 2 staples are used on each side they will bend but rarely break; and if 3 staples are used on each side the growth of bone will be arrested. Blount and co-workers (2) have further stated that it takes about 900 pounds to break a staple under direct pull; however, when inserted in a living bone the staple bends before breaking and this fact alters breaking force materially.

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The present investigation has been directed toward the determination of the force exerted by the growth of epiphyseal bone and more particularly the rate of growth of bone under increasing compression. The behavior of cancellus and cortical bone which is in direct contact and under high compression forces with stainless steel pins or other appliances has been noted. The ability of bone to resume growth after a prolonged period of rest is also presented. This research has now been in progress for more than 5 years and to date 12 calves have been used in this series of experiments (6).

Holstein calves were selected as experimental animals in this investigation for several important reasons. A newborn Holstein calf weighs about 100 pounds, and at the time of these operations it weighed about 150 pounds. Their large size and rapidity of growth make them an ideal animal for the insertion of precise mechanical appliances and accurate growth measurements. These animals are of a pure breed and their growth characteristics are uniform and well known. A point of great importance is the fact that bovine animals do not possess a fibula and the upper tibial epiphysis becomes an isolated unit, readily accessible and of adequate size for the insertion of suitable mechanical devices. Of further note, the capsule of the knee joint does not extend downward over the tibial epiphysis in the same manner that it projects upward around the distal end of the femur. Holsteins have a tractable disposition, accept anesthesia well, and are relatively resistant to infection.

The method used in this investigation employed a tension device strung between the

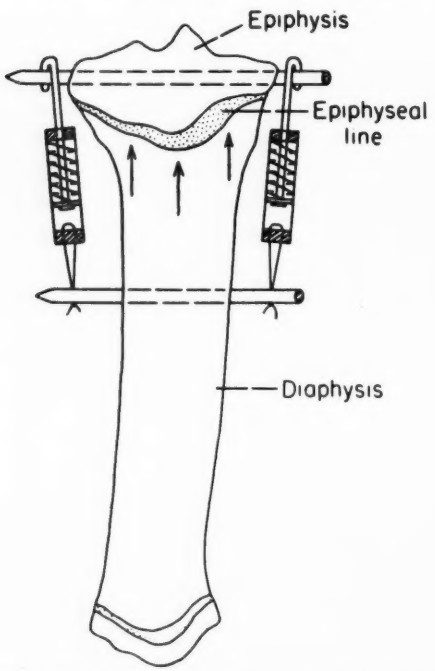


FIG. 1. This diagram shows the spring tension apparatus inserted into the animal. The spring tension devices are strung between the epiphysis and diaphysis. As growth progresses the tension is increased until an equilibrium is established with the growth force equalling the mechanical tension. At this point growth of bone theoretically ceases.

proximal epiphysis and the diaphysis of the tibia. As growth progressed the device was elongated and the apparatus so constructed that elongation increased the compression. As the compression was increased, the epiphyseal plate was placed under an increasing force. Eventually the mechanical and growth forces became equalized. An equilibrium was established and at this point the growth of bone theoretically ceased.

FORCE MEASURING DEVICES

1. The first type of apparatus used is shown in Figure 1; it consists of a heavy steel coil spring encased in a stainless steel cylinder. The upper and lower ends of the cylinder are tightly closed by stainless steel plugs screwed into position. There is a hole in the top plug just large enough to allow the hooked rod to pass through freely and 2 tiny holes in the lower plug admitting the retaining wires. A washer and small nut are attached to the bottom of the rod inside the cylinder; the interior is liberally greased with vaseline allowing freedom of motion within the cylinder and protecting the steel spring from rusting. The entire mechanism is nearly watertight when inserted. A heavy pin is then inserted through the epiphysis and the rods are hooked through holes in this pin as shown while a short but sturdy pin is driven through the midshaft of the tibia. The lower ends of the cylinders are anchored to this diaphyseal pin via heavy wires, threaded double, through holes in the pin. The whole apparatus is placed next to the tibial bone as deeply as possible. Readings are made at regular intervals by relatively high voltage x-rays that penetrate the stainless steel cylinders and show the increasing compression of the springs in the cylinder. The springs used were constructed to specification, giving 1 inch deflection, with a total force of 60 pounds. The limits of the apparatus as read on the compression springs are, therefore, 120 pounds (60 pounds on each side). All exposed parts of the spring tension device were constructed of stainless steel, type No. 316, and no unusual reaction to adjacent soft tissues was noted. No observable erosion of the stainless steel parts was ever detected when they were removed. The coil springs within the cylinder were also in a good stage of preservation and had lost little, if any, of their strength.

Later in this discussion it will be shown that the force exerted by the growing bone exceeded several hundred pounds and it was found then that at this level spring tension devices were no longer practicable.

2. The next apparatus used in this study employed the stress-strain relationship of stainless steel wires. When force is applied to a wire, the wire will stretch. The behavior of the metals in this respect is conventionally expressed by Young's nodulus which is defined by the equation: M equals Fl/sA. F is the force applied, l is the length of the

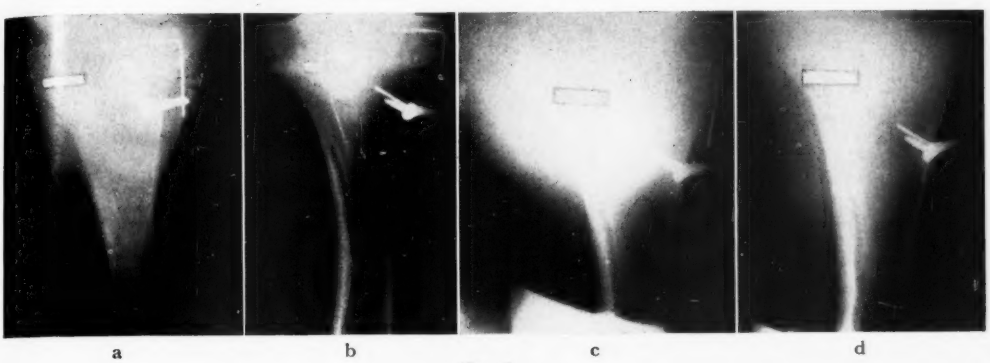


FIG. 2.

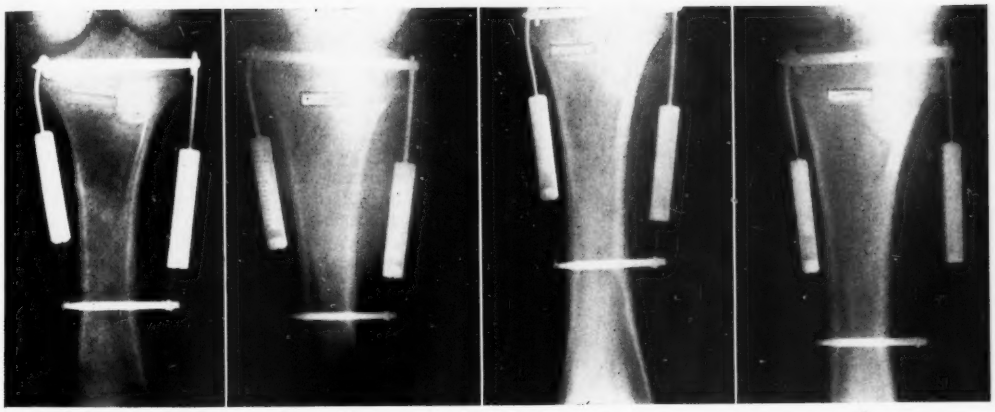


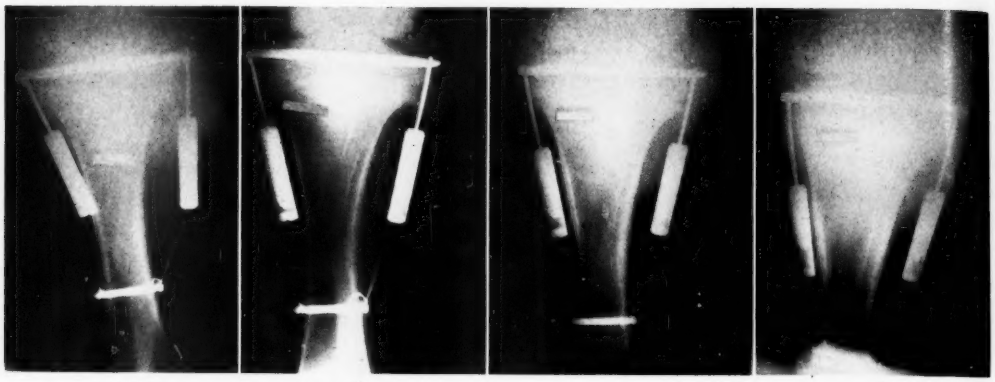
FIG. 3.

FIG. 2. a, The slider type of growth measuring device shows a thin rod bent at right angles, the short upper end is inserted into the epiphysis and the long arm extends downward through a hole in a plate attached to the tibial shaft. (Note: Its tip is well below the plate at its starting point.) b, The tip of the long arm has migrated upward so that it is now at the same level as the small plate in the tibia. c, The tip of the long arm now extends a short distance above the small plate in the tibia. d, The long arm has migrated still farther above the small tibial plate. A large amount of growth has now occurred. This method is accurate to 1 to 2 millimeters growth.

FIG. 3. a, The spring compression apparatus is shown inserted in the animal. (Note: The heavy pin through the epiphysis just above the growth line also the pin through the midshaft and the anchoring wires to the latter.) The springs are visualized within the stainless steel cylinders. The retaining wires are still slack. b, The slack has now been removed from the anchoring wires and the springs are showing a definite degree of compression on each side. c, The compression of the springs has now increased considerably and the force exerted is correspondingly higher. d, One of the retaining wires has now broken and the compression on that side has been released as a result. The other spring has now become nearly fully compressed and is still functioning.

wire, and s is the resulting stretch and A the cross-sectional area. Young's nodulus is constant, however, only for relatively small elongations. When, as in the present investigation, the wire was stretched far beyond the elastic limit and indeed up to the breaking point, Young's nodulus changes materially from its initial value and was therefore not useful.

However, a force elongation relationship for a wire of given dimensions and composition can be determined experimentally up



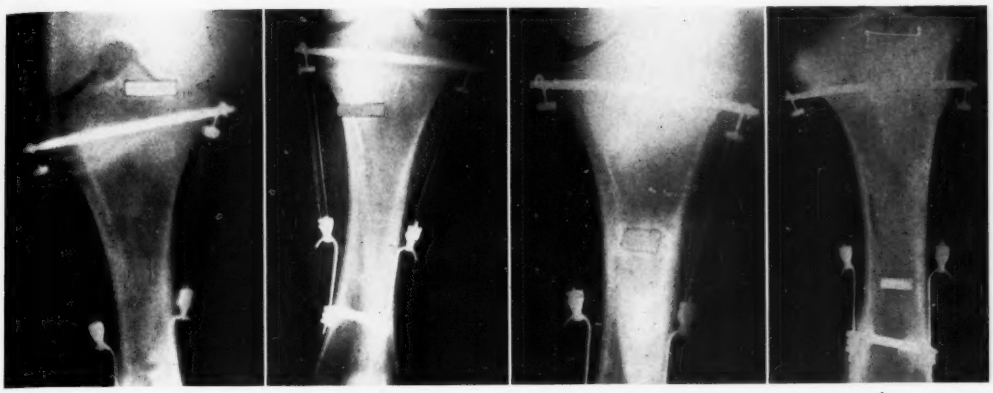
a b c d

e

FIG. 4. a, The compression apparatus has been inserted as in the previous case. There is still a good deal of slack in the anchoring wires and compression has not yet started. b, The slack has been removed from one spring device and compression has started. The other cylinder still shows some slack in the retaining wire. c, There is now moderate compression in both springs and the spring force has been increased proportionately. d, Both springs are now practically closed and the force is approaching 120 pounds. e, The retaining wires have been stretched and broken. The apparatus has been removed and the pin through the epiphysis has remained intact. (Note: The two tibias remain exactly the same length.)

to the breaking point, and this calibration curve (Fig. 6) can then be used to evaluate an unknown force from the measured elongation. This method has been used in the latter part of the investigation when the force has been so great that spring tension devises have no longer been practical.

When a wire of the type and size used in this work has been stretched by an increasing force until the breaking point is reached the accompanying curve (Fig. 6) shows what happens. The wire used in this series of experiments was of molybdenum stainless steel, well tolerated in the tissues. The initial diameter of the wire was 0.028 inch and it had a breaking strength of 70 pounds; at the breaking point the wire has a final diameter of 0.023 inch and has stretched about 40 per cent of its initial length. It will be seen that a strong initial force is necessary to produce a unit increment of length; however, as the wire is stretched beyond the yield point the additional force that is necessary to produce the same increment becomes progressively less until the breaking point is reached. By using multiple parallel strands a very large force can be measured, the same curve holding true in direct proportion to the number of strands used. Thus a battery of 4 parallel strands has a total breaking point of 280 pounds. The identical curve is maintained as for 1 strand even though the force factor is 4 times as great. This method gives an accurate measure of force exerted against the wires being stretched, and in as much as a relatively great increase in length occurs as the breaking point is approached a sharp end point



a b c d

FIG. 5. a, An apparatus with 4 strands on each side has been strung between the epiphysis and midshaft of the tibia. This has a breaking strength of 560 pounds. Note the slack in the wires on both sides. b, The slack has now been removed from the wires and compression is beginning on both sides. c, The heavy pin through the epiphysis is sharply bowed and the pin is migrating across the epiphyseal line. d, The pin has now traversed the growth line with resulting damage to the growth plate.

is attained. Thus measurements can be made with a relatively high degree of accuracy.

A growth measuring device found to be both simple and satisfactory was placed on the control tibia in each animal. The slider type apparatus consists of a thin rod bent at right angles with the short side inserted into the epiphysis and the long arm extending downward. The lower end rides through a small hole in a plate attached to the upper shaft of the tibia. As growth progresses the rod slides upward and the protruding end gives an accurate measure of growth. If, as shown in Figure 2c and d, the lower end eventually is drawn upward beyond the plate, the distance from its tip to the plate can be readily measured. This type apparatus is shown functioning in Figure 2a, b, c, and d. It accurately shows a growth increment of as little as $\frac{1}{25}$ inch (1 mm.).

EXPERIMENTS

It would be superfluous to give a detailed account of each test but 5 such experiments will be presented chronologically as this work progressed.

EXPERIMENT 1. A 6 weeks old bull Holstein calf was operated upon on February 1, 1950. The spring tension was started at zero pounds across the epiphyseal line and the course of this experiment is shown in Figure 3a, b, c, and d. Roentgenograms were taken at regular intervals and it is to be observed that the coil springs became gradually compressed showing that the force across the epiphyseal line was gradually increasing. At the end of 8 weeks the force exerted had attained 75 pounds which was about 10 pounds per square inch cross section. The cross sectional area of the epiphysis of the tibia was about 7 square inches in the animal used. At this time a retaining wire broke on one side releasing the compression on that side. However, the animal was followed for another month during which time the compression on the effective side, or unbroken side, increased from 37 to 52 pounds. It is of interest that the rate of growth on the compression side continued unchanged during the entire test and at practically the same rate as on the control side. The graph showing the increasing compression growth curve accurately fits a straight line (Fig. 7).

EXPERIMENT 2. A 6 weeks old Holstein calf was operated upon on November 2, 1950. In this case the apparatus used was essentially the same as in experiment 1. However, taking advantage of the force attained on the previous test the initial force was set at 65 pounds by compressing the springs to the required degree. There were 4 anchoring wires used with a breaking strength of 70 pounds per strand. On the control side the growth measuring device shown in Figure 2 was used.

The limiting value of the coil springs was 60 pounds on each side or a total of 120 pounds and when the 120 pound level was attained, after a period of about 3 months, the apparatus locked. Cessation of growth,

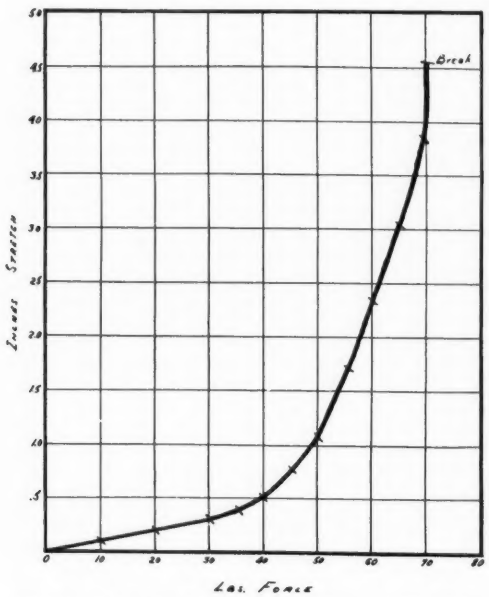


FIG. 6. This curve shows the stress elongation relationship of the stainless steel wire employed. The initial length of the wire was 10 inches and the amount of elongation corresponding to the force exerted is shown. The wire constantly breaks at 70 pounds.

however, did not occur and the 2 stainless steel anchoring and holding wires on each side, which had been carefully anchored without any kinks, finally stretched and broke almost simultaneously—first on one side and then on the other. The breaking strength of these 4 wires had been previously carefully determined and found to be 70 pounds per strand. Therefore, while the limits of the spring tension apparatus were 120 pounds, at which point the apparatus locked and therefore failed to register, the growth of the epiphyseal plate area continued up to about *280 pounds of wire compression*. At this point the wires broke but the epiphyseal growth continued unabated. This entire test lasted for 5 months, taking 2 more months to stretch and break the retaining wires after the coil springs had become fully compressed and locked. We concluded that more than 280 pounds of compression were necessary for epiphyseal growth cessation.

As noted in animal 1, growth on the compression side fitted a straight line precisely and was at the same rate and total amount as on the control side. After both retaining wires had broken, the apparatus was removed and the growth measuring device was inserted on the control side. This animal was followed for more than another month and during this period of time the rate of growth was identical on both sides showing that the rate was in no way altered after release of the compression (Fig. 7). Figure 4 shows the two tibias taken on the same x-ray film with the animal in a standing position and the knees fully extended. It is to be noted that the two tibias have ended up with exactly the same length after the period of 6 months required to complete this test.

EXPERIMENT 3. An 8 weeks old Holstein calf was operated upon October 11, 1951. In this case the stress-elongation relationship of stainless steel wires was employed because, as shown before, the spring compression devices were impractical beyond forces of several hundred pounds. In this test 4 strands of wire 0.028 inch in diameter were used on each side giving a total breaking strength of 560 pounds. The stainless steel pin through the epiphysis was 0.210 inch in diameter and that through the midshaft 0.190 inch in diameter. Figures 5a, b, c, and d show the progress of this test. It will be seen that the slack in the wires was gradually taken up by the growth of bone, and eventually the heavy pin gradually pulled down through the epiphysis and across the epiphyseal line into the diaphysis. The wires did not break but elongated to a point corresponding to a compression force of 300 to 400 pounds. We concluded that a greater compression force was necessary to produce epiphyseal growth cessation in this animal.

EXPERIMENT 4. In this case, animal 3 which now weighed 500 pounds was used for a further compression force experiment. An apparatus with breaking force of 1,120 pounds was inserted across the upper tibial epiphyseal line of the control side. Eight wires, as previously used, and each with a breaking strength of 70 pounds, were stretched between 4 screws above and below the epiphyseal line on each side. This represented a strength of 560 pounds on each side or a total of 1,120 pounds. As soon as the slack was re-

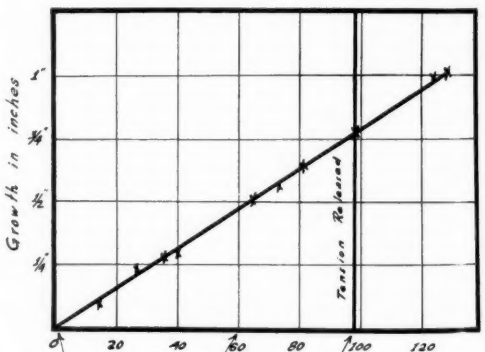


FIG. 7. This graph shows the rate of growth of bone under compression. This is true of both experiment 1 and 2. It shows a straight line relationship confirming an "all or none" law of bone growth.

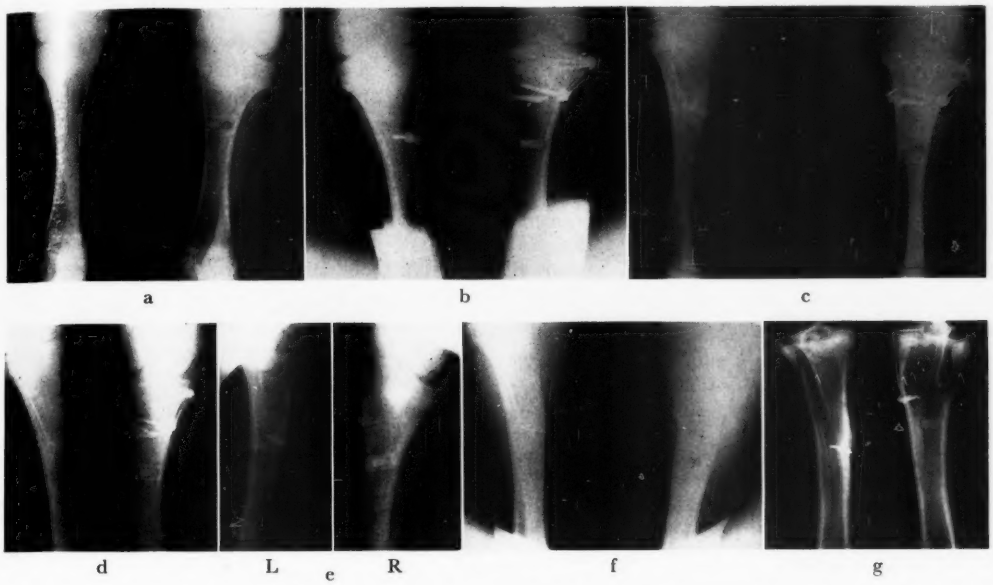


FIG. 8. a, The two tibias of the calf are shown at the beginning of the experiment; they are of equal length. (Note: The calf has no fibula.) b, An apparatus with 4 strands on each side has been inserted across the epiphyseal line of the tibia on the right. Most of the slack has been removed from the wires. A growth measuring device has been inserted in the tibia on the left. c, A high compression force is now recorded in the right tibia and for all practical purposes bone growth has ceased. The tibia on the left continues to grow at a normal rate. d, Complete cessation of growth has been in effect for about 6 months in the right tibia. A marked difference in bone length has resulted. The left tibia continues to grow at a normal rate. e, The compression apparatus has been removed from the right tibia and in its place a growth measuring device has been inserted. The left tibia remains unaffected. f, The slider mechanism on the right is migrating upward rapidly compared with the left side. The previously compressed bone is now growing at an accelerated rate. g, The two tibias after the epiphyseal line has closed. The right tibia has equalized the left, thereby regaining 1⅛ inches. The right tibia is slightly heavier than the left and the diameter is also equal.

moved from this apparatus bone growth ceased completely. The apparatus was retained for several months, but no evidence of growth whatever was observed during this time. The animal was sacrificed after 4 months and the tibia has been preserved. Force measurements could not be made accurately because the strength of the apparatus far exceeded growth force.

EXPERIMENT 5. This experiment has been the longest and most important in our series and lasted for a period of 2 years and 3 months. The data previously determined were carefully analyzed before starting this test. On May 26, 1952, an apparatus similar to the one previously described and capable of measuring a total of 560 pounds was inserted across the upper epiphyseal line of the tibia. Three anchoring screws above and 3 below with 4 wires were used on each side. After a period of several months the slack was taken out of the apparatus and for all practical purposes growth arrest was attained. During the course of the next few months, however, there was some molding of the upper tibial epiphysis with apparently very slight growth progression as the animal increased in size generally. However, the control side continued at a normal rate of growth and after a period of about 9 months there was marked difference in the length of the tibias, the control side being about 1⅛ inches longer than the compression side. For a period of about 6 months practically no growth could be observed on the compression side, but the wires were not broken. Figure 8a, b, c, and d shows the course of the first half of this experiment.

On February 10, 1953, the apparatus was removed and a growth measuring device was inserted on the compression side. The epiphyseal plate was found to be viable after this long period of growth cessation and the growth of the tibia was resumed almost immediately. It is of particular note that this animal was followed for an additional 18 months at which time full bone growth had been attained. During the first 6 months of this interval, comparative growth measurements of the compression and control sides

were made and it was found that growth rate on the compression side was 3 times as great as that of the control side. The animal was thereafter placed out to pasture until full bone maturity was attained at which time the compression side had completely equalized the control side and the two bones became identical in length. Thus, the dormant tibia had grown at a greatly accelerated rate immediately after release of compression force and eventually caught up with the control side that was at one time 1⅛ inches longer. The compression force could be measured with a good degree of accuracy and was equal to 340 pounds at the time of removal. It is of further note that the diameter of the arrested bone was somewhat decreased after cessation of growth occurred, but interestingly enough, the diameter as well as the length eventually attained the dimensions of the control side (Fig. 8e, f, and g).

EXPERIMENT 6. In view of the fact that on the previous experiment an apparatus capable of measuring 560 pounds had resulted in complete cessation of growth and the final reading was 340 pounds at the time of removal, the next experiment employed an apparatus with a limit of 280 pounds. It was believed that this limiting value was very close to the expected growth force and this proved to be the case. The apparatus consisted of 2 anchoring screws above and below the epiphyseal line with 2 strands of wire on each side. The slack was taken out of the apparatus in a matter of a few months and thereafter growth was slowed. The wires were stretched to their breaking point and were broken first on one side and then on the other. A slight degree of slowing of the tibia on the compression side resulted during this experiment. It is quite probable that growth was completely arrested with the animal standing and that it was resumed again with the animal in a prone position. Thus, when the animal was standing, an additional force of approximately one-quarter its weight (about 100 pounds) was added to the recorded compression force, but when prone the total force was equal only to that actually recorded.

DISCUSSION

The foregoing data lead to a number of points of interest. All of the early experiments were devised to measure forces up to approximately 200 pounds and showed the growth of bone under compression to follow a straight line without exception. The rate was the same as on the control side which was under physiologic stress only. These data, therefore, show rather conclusively that the growth of epiphyseal bone follows an "all or none" law with respect to compression forces to a point far beyond physiologic limits. Because of the fact that the animal is part time in a prone position and part time in a standing position in its normal grazing and other activities, the extra weight resulting from gravity complicates the determination of the growth force as it approaches its end point. The information obtained to date does not make it possible to conclude whether or not this "all or none" law of bone growth follows precisely to its final force limit. From the practical aspect, however, it can be stated that an "all or none" law does exist to a point which is far beyond any physiologic limit.

The force of bone growth itself has been determined with a fair degree of accuracy and has been repeatedly approached from a high and low level. In round figures, for the upper tibial epiphysis, it is approximately, but perhaps slightly less than, the total weight of the animal. A value of 340 pounds of actual measurement has been observed. This is equal to 45 pounds per square inch cross-section. It would be expected, though not proved, that the force is in direct proportion to the cross-sectional area, and the clinical significance of this investigation suggests to the authors that first, the smaller the bone the less the growth force, and secondly, that growth arrest in the upper extremity probably requires less compression force than in the lower extremity.

Cessation of growth has been accomplished on 2 occasions and after growth arrest was attained for a relatively long period of time (6 to 7 months) which in humans would be equal to 3 or 4 years, the epiphyseal line was found to be viable and the bone grew at an accelerated rate sufficient to equalize the 1⅛ inches of shortening. The diameter of the arrested bone was also slightly less than on the control side. This dimension, as well as the length, was, however, equalized when the animal had reached full bone maturity.

CONCLUSIONS

There are three fundamental conclusions to be drawn from these experiments:

1. Epiphyseal bone follows an "all or none" law of growth with respect to compressive force exerted against it to a point that is far beyond any physiologic value expected and quite probably to the limit of its force value.

2. The force exerted by the upper tibial epiphysis of the calf is a little less than the total weight of the animal shown by the reading of 340 pounds necessary to produce epiphyseal arrest. This amount is equal to approximately 45 pounds per square inch cross section.

3. The epiphyseal plate has been arrested for a protracted period of time, about 6 months in the calf, which is equal to 3 or 4 years in the human. The plate has remained viable and has thereafter resumed growth sufficient to produce equalization of bone length thereby regaining 1⅛ inches.

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ANALYSIS OF FIVE YEAR SURVIVAL IN CARCINOMA OF THE RECTUM AND RECTOSIGMOID

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THAT RADICAL SURGICAL EXTIRPATION is the treatment of choice for the majority of carcinomas of the rectum and rectosigmoid is a generally accepted concept. However, controversy does arise concerning the optimal type of surgical procedure to be employed. Few physicians will argue the stand that lesions situated near the anus, below or at the level of the levators, or 5 centimeters or less from the dentate margin (three of the descriptive levels in common usage) must be treated by a procedure in which the anal sphincter is sacrificed. For lesions located 20 centimeters or more above the dentate margin, which is well above the peritoneal reflection, most authorities agree that anterior resection with primary anastomosis, with or without proximal colostomy, or an extraperitoneal resection of a modified Mikulicz type is the procedure of choice.

Considerable difference of opinion exists concerning the surgical attack on those lesions in the region of the rectum and rectosigmoid between 6 and 20 centimeters from the dentate margin. Some surgeons consider that one stage combined abdominoperineal resection is the treatment of choice for all malignant lesions in this zone. Others believe that a pull-through type of procedure gives just as satisfactory results from the standpoint of survival and is much more acceptable to the patient. Some surgeons contend that the majority of lesions in the upper part of the rectum and the rectosigmoid, including those situated at the 6 to 10 centimeter level as estimated by proctologic methods, can be extirpated adequately by low anterior resection with or without proximal colostomy. For technical reasons, a procedure that sacrifices the sphincter must be selected in some cases. We think that colostomy with a permanent stoma rarely need be performed when safe and adequate resection and direct anastomosis can be accomplished without tension.

In 1951, one of us (Mayo), with Lee and Davis, reported a study of the records of all patients who had undergone surgical treatment for carcinoma of the rectum and rectosigmoid at the Mayo Clinic in the period from 1945 through 1949. A comparison was made as to the hospital mortality rate among patients on whom anterior resection, one stage combined abdominoperineal resection, and two stage posterior resection, respectively, were done. No significant differences were found in hospital mortality. On the other hand, a comparison made of morbidity, as determined by days of hospitalization, after single stage anterior resection and that after multiple stage anterior resection, disclosed that the multiple stage procedures required, on the average, 30 days more of hospitalization than did the single stage procedures. The patients included in that study now have been followed for a minimum of 5 years, and the survival results are reported herein.

MATERIALS AND METHODS

A review was made of the records of all patients who underwent surgical extirpation of carcinoma of the rectum and rectosigmoid at the Mayo Clinic in the years 1945 through 1949. The patients were grouped as to age and sex, and the surgical specimens were classified as to the preoperative proctoscopic level of the lesion and the presence or ab-

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sence of metastasis to the lymph nodes. We examined the gross specimens removed in the 63 traced cases in which anterior resection had been performed and in which the proctoscopic level of the lesion was between 6 and 9 centimeters from the dentate margin. The position of the lesion in relation to the peritoneal reflection was determined in this group. All cases were further classified as to the type of operative procedure performed, namely low anterior resection, one stage combined abdominoperineal resection, or two stage posterior resection.

Follow-up examination was completed by the Section of Biometry and Medical Statistics of the clinic in 98.7 per cent of the patients. All foreign residents were excluded from the study for obvious reasons. Patients who, in the opinion of the surgeon, had palliative procedures because of palpable hepatic metastatic lesions or malignant tissue that was not excised also were eliminated from this study.

INCIDENCE OF AGE AND SEX

A total of 85.1 per cent of the 1,146 patients included in this study were between the ages of 40 and 69 years; the greatest incidence of the lesions in question occurred in the fifth decade of life and the next greatest in the sixth decade. No significant differences were present in the age distribution in the 3 types of procedures studied (Table I).

There were 717 men and 429 women in the entire group, a ratio of 1.7:1. The sex distribution was equal in the anterior resections; it was 2 men to 1 woman in the remaining two groups (Table II).

It is of more than casual interest that there was almost an equal number of each sex on whom anterior resection (rectosigmoidostomy) could be done, whereas in both one stage and multiple stage combined abdominoperineal resection the ratio was 2 men to 1 woman. It is also important to keep in mind the aforementioned fact that carcinoma of the rectum had a ratio in this series of 1.7 men to 1 woman. Since there were only 3 patients who had lesions below the 6 centimeter level on whom anterior resection was performed, a comparison was made of all patients in whom the lower edge of the lesion was between 6 and 25 centimeters from the dentate margin. Here again, the ratio was 1 man to 1 woman in the group treated by anterior resection and 2 men to 1 woman in the group treated by one stage or multiple stage combined abdominoperineal resection. Thus, it becomes apparent that either more women or less men receive the benefit of procedures that save the sphincter. Since 302 patients who had lesions above the 5 centimeter level were treated by anterior resection and 478 who had similarly situated lesions were treated by a sphincter-sacrificing procedure, it becomes evident that more men are treated by sphincter-sacrificing operations. This variation is thought to be due, at least in part, to the technical difficulties associated with the shape of the male pelvis in the performance of low anastomosis. That this difficulty has been partially overcome on the surgical service of one of us (Mayo) by the use of specially designed long instruments is indicated by the ratio of 1.2 men

TABLE I.—INCIDENCE BY AGE AND OPERATIVE PROCEDURE

Age, yrs.	*Anterior resection*		*One stage combined abdominoperineal resection*		*Two stage posterior resection*	
	Patients	*Per cent*	*Patients*	*Per cent*	*Patients*	*Per cent*
20–29	1	0.3	10	1.6	2	0.9
30–39	17	5.3	28	4.6	6	2.8
40–49	50	15.7	96	15.7	38	17.7
50–59	120	37.6	221	36.1	76	35.3
60–69	95	29.8	204	33.3	75	34.9
70–79	34	10.7	52	8.5	18	8.4
80–89	2	0.6	1	0.2	0	—
Total	319	100.0	612	100.0	215	100.0

TABLE II.—INCIDENCE BY SEX AND OPERATIVE PROCEDURE

Sex	*Anterior resection*		*One stage combined abdominoperineal resection*		*Two stage posterior resection*	
	Patients	*Per cent*	*Patients*	*Per cent*	*Patients*	*Per cent*
Male	160	50.2	408	66.7	149	69.3
Female	159	49.8	204	33.3	66	30.7
Total	319	100.0	612	100.0	215	100.0
Ratio M:F	1:1		2:1		2.3:1	

TABLE III.—INCIDENCE BY OPERATION AND PROCTOSCOPIC LEVEL OF LESION

Distance from dentate margin, cm.	*Anterior resection*		*One stage combined abdominoperineal resection*		*Two stage posterior resection*	
	Patients	*Per cent*	*Patients*	*Per cent*	*Patients*	*Per cent*
0–5	3	0.9	264	43.1	85	39.5
6–9	68	21.3	234	38.2	90	41.9
10–14	224	70.3	105	17.2	38	17.7
15–19	18	5.6	8	1.3	2	0.9
20+	6	1.9	1	0.2	0	—
Total	319	100.0	612	100.0	215	100.0

to 1 woman in the low anterior resections performed on his service.

DISTRIBUTION BY PROCTOSCOPIC LEVEL

As would be expected, in about half the cases in which one stage combined abdominoperineal resection or two stage posterior resection was performed, the growths were in the distal 5 centimeters of the rectum, as compared to only 3 cases in which anterior resection was performed for lesions in this segment of the colon. A sufficient number of lesions occurred at the most controversial levels (6 through 9 cm. and 10 through 14 cm. from the dentate margin) to allow statistically significant comparisons (Table III).

INCIDENCE OF METASTASIS

The incidence of metastasis to the lymph nodes in each of the 3 types of surgical procedures studied was in the range of 45 to 50 per cent. There was no significant variation in the number of cases with and without nodal metastasis in the various segments of the rectum and sigmoid studied (Table IV).

INCIDENCE BY GRADE OF MALIGNANCY

All lesions were classified on the basis of microscopic degree of cellular differentiation as described by Broders (Table V). In the over-all group, 88.8 per cent of the lesions were of low grade malignancy (grades 1 and 2) and 11.2 per cent were of high grade malignancy (grades 3 and 4). No significant difference was noted in the distribution by grade of malignancy among the lesions according to the type of resection.

SURVIVAL

The over-all 5 year survival rate for the entire group of traced patients, regardless of the level of the lesion or type of operative procedure, was 52.5 per cent. This figure agrees with the generally accepted survival rate in carcinoma of the colon. In this series, the group of patients who underwent anterior resection had the highest 5 year survival rate and those who underwent two stage posterior resection had the lowest. This undoubtedly is explained, at least in part, by the factor of surgical selection that enters into the decision to perform a multiple stage procedure. Age is not considered a significant factor in the analysis of the differences in survival, since the distribution by decades was essentially the same for all groups. Neither is the grade of malignancy of the lesion a significant factor in this analysis, as the distribution was essentially the same in each group studied.

Regardless of the type of procedure performed, the 5 year survival rate in women was about 6 percentage points better than it was in men (Table VI). This follows the general trend in the population as a whole; rates in almost all the 64 major causes of death in the United States in 1950 were higher in males than in females, according to Sowder.

The 5 year survival rates in each group are compared in Table VII. Of significance is the fact that the survival rate (58.5 per cent) in all patients treated by anterior resection was 6.8 percentage points greater than it was in those patients on whom one stage combined abdominoperineal resection was done and 12.5 percentage points greater than in the group of patients for whom two stage posterior resection was selected as the operation of choice. This difference is essentially the same when comparison is made of the same general groups with and without metastasis.

It has been generally thought that those lesions near the anus, in the lower 5 centimeters of the rectum, have the worst prognosis. This has not proved to be true in this

TABLE IV.—INCIDENCE OF METASTASIS BY OPERATION AND PROCTOSCOPIC LEVEL OF LESION

Distance from dentate margin, cm.	Anterior resection				One stage combined abdominoperineal resection				Two stage posterior resection			
	Metastasis		No metastasis		Metastasis		No metastasis		Metastasis		No metastasis	
	Patients	Per cent	Patients	Per cent	Patients	Per cent	Patients	Per cent	Patients	Per cent	Patients	Per cent
0- 5	2	1.3	1	0.6	103	35.6	161	49.8	40	39.6	45	39.4
6- 9	34	22.8	34	20.0	122	42.2	112	34.7	41	40.6	49	43.0
10-14	102	68.5	122	71.7	56	19.4	49	15.2	19	18.8	19	16.7
15-19	7	4.7	11	6.5	8	2.8	0	—	1	1.0	1	0.9
20+	4	2.7	2	1.2	0	—	1	0.3	0	—	0	—
Total	149	100.0	170	100.0	289	100.0	323	100.0	101	100.0	114	100.0

series (Table VIII). The patients on whom anterior resection was performed are disregarded in this analysis because of the small number who had lesions in this segment. Of the large group of patients on whom one stage combined resection was done and whose lesions occurred in the distal 5 centimeters of the rectum, 50.4 per cent lived 5 years or more after operation. This is only 4.4 percentage points less than the rate in similarly treated patients who had lesions from 6 to 9 centimeters from the dentate margin and is 2.4 percentage points more than in similarly treated patients whose lesions were 10 to 14 centimeters from the dentate margin. This same distribution occurs in the smaller group of patients who had two stage posterior resection. Significant differences in survival rates were absent in the patients who did not have metastasis, who had been treated by combined abdominoperineal resection, and in whom the lesion occurred at levels of 0 to 5, 6 to 9, and 10 to 14 centimeters, respectively, from the dentate margin.

The 5 year survival rate was 24.5 per cent in the 98 followed patients in whom combined abdominoperineal resection was performed, in whom the lower edge of the lesion was 0 to 5 centimeters from the dentate margin, and in whom nodal metastasis was present; this compares to a rate of 25.6 per cent for patients with similar lesions treated by two stage posterior resection. The results at other levels were consistently poor in the patients on whom a two stage posterior resection was performed when metastasis had occurred. However, in the absence of metastasis, we found comparatively little difference in results between patients treated by means of two stage posterior resection and those who had one stage combined resection. Since only patients with lesions that do not extend below 6 centimeters from the dentate margin are suitable for sphincter-saving procedures, they should be considered separately. The 5 year survival rate of patients with lesions between 6 and 25 centimeters from the dentate margin treated by anterior resection is 6.4 percentage points greater than that of patients with similar lesions treated by one stage combined abdominoperineal resection and is 12.3 percentage points greater than in those treated by two stage posterior resection. This difference is also manifest when the groups are studied on the basis of nodal metastasis (Table IX).

Patients with lesions located more than 15 centimeters from the dentate margin are rarely treated at the clinic by other than anterior resection. The proctoscopic level of the lesion was from 6 to 15 centimeters above the dentate margin in 91.6 per cent of the patients in this series treated by anterior resection. The survival rates of patients with lesions in this controversial region are compared in Table IX. It will be noted that 58.9 per cent of the patients who underwent anterior resection, 52.7 per cent

TABLE V.—INCIDENCE BY OPERATION AND MICROSCOPIC GRADE OF MALIGNANCY (BRODERS)

Malignancy, grade	Anterior resection		One stage combined abdominoperineal resection		Two stage posterior resection	
	Patients	Per cent	Patients	Per cent	Patients	Per cent
1	125	39.2	236	38.6	95	44.2
2	166	52.0	301	49.1	95	44.2
3	25	7.8	58	9.5	15	7.0
4	3	1.0	17	2.8	10	4.6
Total	319	100.0	612	100.0	215	100.0

TABLE VI.—SURVIVAL ACCORDING TO SEX

	Men				Women			
			Lived 5 yrs. or more after operation				Lived 5 yrs. or more after operation	
Surgical procedure	*Total*	*Traced*	*Patients*	*Per cent**	*Total*	*Traced*	*Patients*	*Per cent**
Anterior resection	152	150	83	55.3	154	152	94	61.8
Combined abdominoperineal resection	385	383	191	49.9	200	197	109	55.3
Posterior resection	148	146	64	43.8	65	65	33	50.8

*Based on traced patients; inquiry as of January 1, 1955. Hospital deaths are excluded in the calculation of survival rates.

of those treated by one stage combined abdominoperineal resection, and 46.8 per cent of those who had two stage posterior resection survived 5 years or more; again, the differences are about 6 and 12 percentage points, respectively. In the absence of metastasis, the 5 year survival rate of the group treated by anterior resection is better by 7.2 percentage points than that of the group treated by one stage combined abdominoperineal resection.

The most controversial group is composed of those patients in whom the lower edge of the lesion is found by proctoscopic examination to fall between 6 and 9 centimeters from the dentate margin. The results of treatment of patients with such lesions differed little among the 3 procedures; 50.8 per cent of such patients treated by anterior resection, 54.8 per cent of those treated by one stage combined abdominoperineal resection, and 50 per cent of those treated by two stage posterior resection survived 5 years or more after operation (Table VIII). When only the patients who had nodal metastasis were considered, similar differences were noted between those treated by anterior resection and those who underwent one stage combined resection. However, the 25 per cent 5 year survival rate in patients treated by two stage posterior resection was significantly lower.

COMMENT

The final selection as to the type of operative procedure to be performed in the surgical treatment of carcinoma of the colon can be made only by the surgeon. No criticism can be made of the selection of a sphincter-sacrificing technique for lesions in the region of the anus and in the distal 5 centimeters of the rectum. Decision as to whether a one stage or two stage operation should be performed will depend largely upon the condition of the patient at the time of operation.

In lesions above the 5 centimeter level, the final decision as to the type of procedure must be made by the surgeon only after the tumor has been exposed. In making this decision, he must consider the patient from the standpoint of both the immediate present and the future. His decision must be based on consideration of several factors, the first and most important of which is the possibility of cure. This includes the technical feasibility of removing a fixed lesion from above and of clamping and excising the intestine far enough below the lesion to accomplish complete extirpation of any distal mucosal spread and to minimize seeding of malignant cells. Secondly, and nearly as important a consideration as cure, is the factor of the future comfort and convenience of the patient. Obviously, a patient

TABLE VII.—FIVE YEAR SURVIVAL RATES ACCORDING TO OPERATION AND METASTASIS

	Anterior resection				One stage combined abdominoperineal resection				Two stage posterior resection			
			Lived 5 yrs. or more after operation				Lived 5 yrs. or more after operation				Lived 5 yrs. or more after operation	
	Total	*Traced*	*Patients*	*Per cent**	*Total*	*Traced*	*Patients*	*Per cent**	*Total*	*Traced*	*Patients*	*Per cent**
Metastasis	146	144	61	42.4	275	273	94	34.4	100	100	26	26.0
No metastasis	160	155	114	73.5	310	307	206	67.1	113	111	71	64.0
Total	306	299	175	58.5	585	580	300	51.7	213	211	97	46.0

*Based on traced patients; inquiry as of January 1, 1955. Hospital deaths are excluded in the calculation of survival rates.

TABLE VIII.—FIVE YEAR SURVIVAL RATES ACCORDING TO OPERATION AND LEVEL OF LESION

Distance from dentate margin, cm.	Anterior resection				One stage combined abdominoperineal resection				Two stage posterior resection			
	Total	Traced	Lived 5 yrs. or more after operation Patients	Per cent*	Total	Traced	Lived 5 yrs. or more after operation Patients	Per cent*	Total	Traced	Lived 5 yrs. or more after operation Patients	Per cent*
0- 5	3	3	0	0	255	254	128	50.4	85	85	38	44.7
6- 9	63	63	32	50.8	221	219	120	54.8	88	86	43	50.0
10-14	218	212	130	61.3	100	98	47	48.0	38	38	15	39.5
15-19	17	16	10	62.5	8	8	4	50.0	2	2	1	50.0
20+	5	5	3	60.0	1	1	1	100.0	0	0	0	—
Total	306	299	175	58.5	585	580	300	51.7	213	211	97	46.0

*Based on traced patients; inquiry as of January 1, 1955. Hospital deaths are excluded in the calculation of survival rates.

should not be subjected to a procedure that would materially lessen his chances of cure, but every consideration should be given to his future comfort by avoidance of colostomy with a permanent stoma when those chances are not compromised. The third factor is the immediate condition of the patient and his ability to withstand a somewhat more prolonged procedure; this, however, should be a rare consideration. The technical difficulty with which a procedure can be accomplished should be the last consideration. No patient should be forced to acquire a permanent colonic stoma simply because it would be difficult to perform a sphincter-saving procedure. On the other hand, if conditions are such, as in extremely obese patients, that an accurate anastomosis cannot be performed, a procedure other than low anterior resection should be selected.

From the standpoint of survival, it is evident from this study that a sphincter-sacrificing procedure offers little more chance for 5 year survival than does anterior resection in lesions that occur more than 5 centimeters from the dentate margin. In the most highly controversial group, in which the lower edge of the lesion is situated 6 to 9 centimeters from the dentate margin, the difference in survival rates between patients treated by anterior resection and by one stage combined resection is insignificant. Even though our patients treated by one stage combined resection had a 5 year survival rate that was 4 percentage points greater than in those treated by anterior resection, few patients would be unwilling to take this small risk to retain normal sphincteric control.

Anterior resection has been found to be as effective for cure, based on 5 year survival rates, as is either of the other 2 procedures studied. This pattern is consistent in comparison of patients with lesions at various levels. With regard to concomitant proximal colostomy, it has been shown previously (3) that its use produces no significant decrease in operative mortality rates but does cause the hospital stay to be more than doubled

TABLE IX.—FIVE YEAR SURVIVAL RATES ACCORDING TO OPERATION AND METASTASIS IN LESIONS 6 TO 15 CENTIMETERS FROM THE DENTATE MARGIN

Distance from dentate margin, cm.	Anterior resection				One stage combined abdominoperineal resection				Two stage posterior resection			
	Total	Traced	Lived 5 yrs. or more after operation Patients	Per cent*	Total	Traced	Lived 5 yrs. or more after operation Patients	Per cent*	Total	Traced	Lived 5 yrs. or more after operation Patients	Per cent*
Without metastasis	148	144	106	73.6	155	152	102	67.1	67	65	43	66.2
6- 9	31	31	20	64.5	109	108	74	68.5	48	46	33	71.7
10-14	117	113	86	76.1	46	44	28	63.6	19	19	10	52.6
With metastasis	133	131	56	42.7	166	165	65	39.4	59	59	15	25.4
6- 9	32	32	12	37.5	112	111	46	41.4	40	40	10	25.0
10-14	101	99	44	44.4	54	54	19	35.2	19	19	5	26.3
Total (6-14)	281	275	162	58.9	321	317	167	52.7	126	124	58	46.8

*Based on traced patients; inquiry as of January 1, 1955. Hospital deaths are excluded in the calculation of survival rates.

because of the multiple procedures required. Our study disclosed no difference in survival rates when anterior resection was done in one, or in more than one, stage; 59.2 per cent of patients treated by multiple stage anterior resection and 59.4 per cent of those treated by single stage anterior resection survived 5 years or more following the operation.

In patients in whom malignant lesions were situated 6 to 9 centimeters from the dentate margin, Waugh and associates found a 5 year survival rate of 51.5 per cent after abdominoperineal resection with sphincteric preservation ("pull-through"). This compares favorably with 5 year survival rates of 50.8 per cent after anterior resection and 54.8 per cent after combined abdominoperineal resection for similarly situated lesions in our study. There appears to be little reason to think that the sphincter must be sacrificed in patients who have lesions at this level.

Kirklin and co-workers studied a group of patients treated by abdominoperineal resection in whom the lesions were either completely above or below the peritoneal reflection; significant differences in survival rates between the two groups were absent. David and Gilchrist found a 13 per cent better survival rate in patients whose lesions were above the peritoneal reflection as compared to those with lesions below this landmark. In our study, as mentioned previously, the specimens from patients in whom the lower edge of the lesion was reported by the proctoscopist to be between 6 and 9 centimeters from the dentate margin and who were treated by anterior resection were examined to determine the relation of the lesion in respect to the peritoneal reflection. In 20 specimens, the lesion was completely below the peritoneal reflection and 60 per cent of these patients survived for 5 years. In 16, the lesion occurred completely above the peritoneal reflection, and 43.7 per cent of these patients survived for 5 years. In the remaining 27 specimens, the lesion involved the region of the peritoneal reflection and extended both above and below; the survival rate in these patients was 48.2 per cent. Such small numbers of patients are included in each category that these results cannot be considered to be statistically significant. However, these findings appear to indicate that the level of the lesion in relation to the peritoneal reflection is of little prognostic significance.

SUMMARY AND CONCLUSIONS

A comparison of the survival rates of 1,146 patients with carcinoma of the rectum and rectosigmoid treated by anterior resection, by one stage combined abdominoperineal resection, or by posterior resection is presented. The influence of metastasis to the regional lymph nodes, of the grade of malignancy of the lesion, of the proctoscopic level of the lesion, and of the location of the tumor in relation to the peritoneal reflection is analyzed and a comparison made among the 3 operative procedures.

The results of these survival studies in the controversial groups, that is, patients whose lesions are located between 6 and 15 centimeters from the dentate margin, indicate that a sphincter-preserving procedure, such as anterior resection, is as curative as is one stage combined abdominoperineal resection or two stage posterior resection.

The level of the lesion in relation to the peritoneal reflection has little influence on the survival rates.

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CLINICAL ACID-BASE REGULATION— THE BRONSTED SCHEMA

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OF THE LABORATORY FEATURES of surgical care now in common use, those relating to acid-base disorders are perhaps least satisfactory and most inconclusive. Yet the clinical problems remain pressing: renal acidosis, obstructing duodenal ulcer, hypokalemic alkalosis, respiratory acidosis, dehydration, ketosis. All these demand accurate definition of the metabolic and respiratory acid-base problems and a knowledge of blood buffers, renal compensations, and electrolyte shifts for optimal preoperative and postoperative surgical care.

Acid-base chemistry is the study of factors influencing hydrogen ion concentration. There is increasing feeling that the use of a framework which focuses on the hydrogen ion would greatly facilitate the clinical understanding of acid-base problems. Such a framework is provided by the Bronsted theory.

The Bronsted schema considers acids as hydrogen ion donors and bases as hydrogen ion acceptors. The intrinsic simplicity of this concept gives the study of acid-base regulation a unity and comprehensive character lacking in much of present clinical thought —where such different species as sodium and bicarbonate ions are "bases" and chloride ion is an "acid." Introduction of the Bronsted concept not only eliminates some of this confusion but, in focusing on the hydrogen ion, makes concomitant electrolyte changes more easily understood.[1]

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Editors' note: This article was written by two fourth year students at Harvard Medical School. It represents their attempt to clarify the teaching and terminology of acid-base balance in such a way as to make the care of the patient easier. This is not a report of research work, which is original, but instead represents what the Editors believe to be a valuable aid to medical students and surgeons in teaching and at the bedside.

THE BRONSTED THEORY

Bronsted[2] defines an acid as a hydrogen ion (proton) donor and a base as a hydrogen ion acceptor. Neutral molecules, cations, or anions can be acids; likewise, any of these species can be bases. Thus, in general:

Acid (proton donor)	⇌	*Base* (proton acceptor)	+	H^{+}[3] (proton)
H_2CO_3	⇌	HCO_3^-	+	H^+
NH_4^+[4]	⇌	NH_3	+	H^+
$H_2PO_4^-$	⇌	$HPO_4^=$	+	H^+

A strong acid will readily donate its proton; its conjugate base will be weak. A strong base will show a high proton affinity; its conjugate acid will be weak. The strength of an acid may be expressed in terms of the equilibrium constant, K, for its dissociation:

$$K = \frac{[\text{Base}]\,[H^+]}{[\text{Acid}]}$$

Now, solving for $[H^+]$, one sees that

$$[H^+] = K\frac{[\text{Acid}]}{[\text{Base}]}$$

The larger the value of K, the greater the hydrogen ion concentration contributed by

[1] The focus on the hydrogen ion, so central in a Bronsted approach, does not imply that acid-base alterations occur because p_H is the parameter "the body is trying to regulate." Rather, this approach clarifies these processes and their concomitant changes, whatever the "cause."

[2] BRONSTED, J. N. The conception of acids and bases. Rec. Trav. Chim., 1923, 42: 718.

[3] In aqueous solutions the proton exists as the oxonium ion, H_3O^+. For simplicity, however, we will represent it as the unhydrated cation.

[4] Although ammonium ion dissociation is negligible at physiologic p_H, ammonia is removed by the liver in vivo and dissociation is favored.

a given amount of acid; or, in other words, the larger the value of K, the stronger the acid.

When the negative log is taken, it follows that

$$(1) \qquad pH = pK + \log \frac{[Base]}{[Acid]}$$

Since pK is the negative log of K, acid strength increases as pK decreases. The pK of any acid is numerically equal to the *p*H at which the concentration of the acid is equal to that of its conjugate base, viz., [base]/[acid] = 1, the term log [base]/[acid] is zero.

NORMAL ACID-BASE PHYSIOLOGY

Renal regulation of blood hydrogen ion concentration. In the course of normal metabolism, the body produces a net excess of acid. The kidney compensates for this by the release of base into the bloodstream, with a concomitant excretion of acid.

The role of phosphate. The renal tubular cell handles the normal net excess of acid by liberation of bicarbonate ion into the blood. This base may be considered to associate with the excess protons of plasma; the carbonic acid so formed is carried to the lungs and, in essence, excreted as carbon dioxide is exhaled.

Despite the body's potentially limitless supply of carbon dioxide from cellular metabolism, and hence its vast potential reservoir of hydrogen and bicarbonate ions, the equation below demands that each hydrogen ion produced or excreted at the lungs must be accompanied by a bicarbonate ion:

$$CO_2 + H_2O \overset{CA}{\rightleftharpoons} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

When either hydrogen ion or bicarbonate ion is selectively added to or subtracted from this system, there must be an alteration of serum *p*H unless there is renal or pulmonary compensation.

The bicarbonate secreted into the blood arises from the dissociation of carbonic acid; this carbonic acid, in turn, is formed from carbon dioxide and water—a reaction catalyzed by the carbonic anhydrase (CA) of the renal tubular cell. The proton simultaneously released by the carbonic acid dissociation is secreted into the lumen of the distal tubule where it is excreted (Fig. 1).

At a normal blood *p*H, 7.40, it can be shown that there is about 5 times as much monohydrogen phosphate, $HPO_4^=$, as there is dihydrogen phosphate, $H_2PO_4^-$.

$$pH = pK_2 + \log \frac{[HPO_4^=]}{[H_2PO_4^-]}$$

$$7.4 = 6.7 + \log \frac{[HPO_4^=]}{[H_2PO_4^-]}$$

$$[HPO_4^=] = 5\,[H_2PO_4^-]$$

Urine, however, is more acidic than blood and the *p*H of urine can range as low as 4.5. At these more acidic *p*H values, in accordance with equation (1), the relative concentration of dihydrogen phosphate increases. Thus, at a typical urinary *p*H, 5.5, there is 16 times as much of the more highly protonated species.

$$5.5 = 6.7 + \log \frac{[HPO_4^=]}{[H_2PO_4^-]}$$

$$5.5 = 6.7 - \log \frac{[H_2PO_4^-]}{[HPO_4^=]}$$

$$[H_2PO_4^-] = 16\,[HPO_4^=]$$

This dramatic change is achieved via conversion of monohydrogen phosphate to dihydrogen phosphate by addition of a proton.

$$HPO_4^= + H^+ \rightarrow H_2PO_4^-$$

This excretion of dihydrogen phosphate provides a major pathway for the elimination of protons formed by the carbonic anhydrase mechanism of the renal tubular cell.

The role of ammonia. The ammonium ion, NH_4^+, is the other principal vehicle for proton excretion by the kidney. Ammonia formed in the kidney from oxidative deamination of amino acids or from hydrolysis of blood glutamine, is converted either to urea (in the liver) or, by combination with a proton, to ammonium ion (in the kidney). Since the total daily urinary excretion of nitrogen is fairly constant, it follows that the level of

urea in the urine varies inversely with the ammonium ion excretion. In particular, in acidosis, where protons must be eliminated, ammonium ion synthesis and excretion are favored; in alkalosis, however, protons are conserved, little or no ammonium ion is synthesized, and urea excretion is increased accordingly.

As with dihydrogen phosphate, the proton for ammonium ion synthesis arises from the dissociation of carbonic acid with the concomitant release of the base, bicarbonate ion, into the blood. Thus, the kidney compensates for the acid produced in the course of normal metabolism through a carbonic anhydrase catalyzed mechanism.

If the carbonic anhydrase system is not functioning adequately, or has been inhibited [as by acetazoleamide (diamox®)], an acidosis will result. Similarly, the acidosis observed in the Fanconi syndrome and in "renal tubular acidosis" may be due to a congenital defect in the carbonic anhydrase mechanism. Nonspecific damage to the renal tubules may also interfere with acidification of the urine. Thus in pyelonephritis following urinary tract infection or bilateral ureterosigmoidostomy, acidosis is not uncommon.

Ventilatory regulation of blood hydrogen ion concentration—carbon dioxide transport. Normally, about 10 millimoles of carbon dioxide must be transported to the lungs for excretion every minute. Simple physical solution, depending as it does on the difference in carbon dioxide tension between arterial (alveolar pCO_2) and venous (tissue pCO_2) blood, accounts for only some 0.5 millimole per minute (or about 5 per cent) of the carbon dioxide transported. Another 20 per cent is transported as a carbamino compound with hemoglobin and with plasma proteins. The bulk, some 75 per cent, is carried by the blood as bicarbonate.

Carbon dioxide from cellular metabolism diffuses into the plasma. As the carbon dioxide concentration in plasma increases, there is diffusion into the red cell. In the red cell, the enzyme carbonic anhydrase

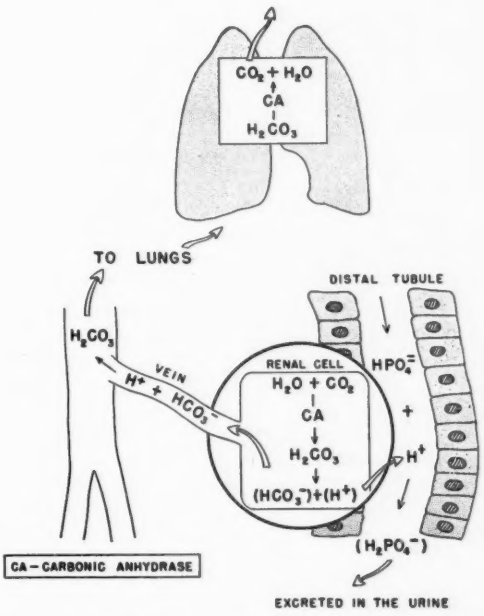

FIG. 1. Renal regulation of blood hydrogen ion concentration—proton excretion with phosphate via the carbonic anhydrase system.

reversibly catalyzes the rapid hydration of this carbon dioxide:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3$$

As we have seen, most of the carbonic acid at physiologic *p*H is dissociated:[5]

$$H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

Indeed, at *p*H 7.4, it can be calculated from the Henderson-Hasselbalch equation (viz., equation 2) that there is 20 times as much bicarbonate as carbonic acid.

$$(2) \quad \begin{aligned} pH &= pK_1 + \log [HCO_3^-]/[H_2CO_3] \\ 7.39 &= 6.10 + \log [HCO_3^-]/[H_2CO_3] \\ 1.29 &= \log [HCO_3^-]/[H_2CO_3] \\ 20 &= [HCO_3^-]/[H_2CO_3] \end{aligned}$$

Since the dissociation of carbonic acid to bicarbonate is accompanied by the liberation of a hydrogen ion, and since there is no

[5]Bicarbonate ion, the conjugate base of carbonic acid, is itself an acid, but a very weak one.

$$HCO_3^- \rightleftharpoons CO_3^= + H^+; \quad pK_2 = 10.2$$

At physiologic *p*H, therefore, its dissociation is so slight that its role as a hydrogen ion donor can be neglected.

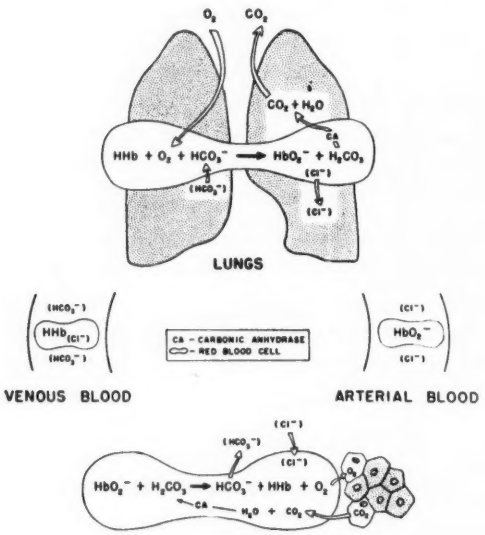

FIG. 2. Oxygen and carbon dioxide transport—the role of hemoglobin.

appreciable increase (*p*H 7.40 to *p*H 7.38) observed in hydrogen ion concentration ("isohydric change"), as carbon dioxide is taken up by the venous blood, we must conclude that the hydrogen ion is being neutralized by base. This base is reduced hemoglobin anion (Hb^-).[6]

Oxyhemoglobin is a stronger acid than reduced hemoglobin.

$$HHbO_2 \rightleftharpoons H^+ + HbO_2^- \quad (pK = 6.60)$$
$$HHb \rightleftharpoons H^+ + Hb^- \quad (pK = 7.85)$$

In other words, reduced hemoglobin anion is a stronger base than oxyhemoglobin anion. Consequently, at the tissues, where oxyhemoglobin becomes reduced hemoglobin, the stronger base, reduced hemoglobin anion, readily neutralizes the proton from carbonic acid dissociation. Thus, the net reaction in the red cell is

$$H_2CO_3 + Hb^- \rightarrow HHb + HCO_3^-$$

and the net change in hydrogen ion concentration is negligible (Fig. 2).

[6]Other bases (viz., plasma protein and phosphate) play a minor role.

As the concentration of bicarbonate increases within the red cell, bicarbonate diffuses into the plasma, impelled by this concentration gradient. The combination of the base (reduced hemoglobin anion) with the hydrogen ion from the carbonic acid dissociation causes a decrease in the net negative charge inside the red cell. This alteration in electroneutrality is adjusted by the migration of the chloride anion from plasma into the red cell (Fig. 2). The final quantitative distribution of electrolytes between plasma and erythrocyte is determined by the Donnan equilibrium.

Sodium and potassium in carbon dioxide transport. It is unnecessary to assign a primary role in carbon dioxide transport to either sodium or potassium ion; they can be considered as counter ions to the anions in the maintenance of electroneutrality. The Bronsted theory obviates the need for complicating the equations of carbon dioxide transport with a cation notation.

CLINICAL MEASUREMENT OF ACID-BASE STATUS

Hydrogen ion concentration, carbon dioxide content, and carbon dioxide combining power are parameters frequently measured in the clinical assessment of acid-base status. The utilization of such data is apparent from expansion of the Henderson-Hasselbalch equation.

Since the concentration of carbonic acid is proportional to the concentration of dissolved carbon dioxide, this proportionality constant can be included in the equilibrium constant. Equation (2) can now be rewritten in terms of the concentration of dissolved carbon dioxide.

$$(3) \qquad pH = pK_1' + \log [HCO_3^-]/[CO_2]_{\text{dissolved}}$$

Recognizing that the concentration of dissolved carbon dioxide is proportional to the partial pressure of carbon dioxide, pCO_2, in equilibrium with the solution,

$$(4) \qquad [CO_2]\ \text{dissolved} = f \cdot pCO_2$$

we can further rewrite the Henderson-Hasselbalch equation:

(5) $pH = pK_1' + \log [HCO_3^-]/f \cdot pCO_2$

From equation (5) it follows that if alveolar (and hence arterial) pCO_2 is lowered (as by hyperventilation) the *p*H of the blood will tend to rise. Similarly, if alveolar pCO_2 is elevated (as in hypoventilation), blood *p*H will decline.

Carbon dioxide content. The carbon dioxide content (total CO_2) is the total carbon dioxide liberated by acidification of serum and is therefore the sum of all forms of carbon dioxide in serum, viz., dissolved carbon dioxide and bicarbonate. (There is a small amount of carbamino-CO_2 in serum but this can be neglected.) Expressed algebraically, this relation becomes:

(6) $(\text{total } CO_2) = [HCO_3^-] + [CO_2]_{\text{dissolved}}$

Now, substituting equations (6) and (4) into (5), we have:

(7) $pH = pK_1' + \log [\text{total } CO_2] - f \cdot pCO_2/f \cdot pCO_2$

With constant alveolar ventilation and hence an unchanged pCO_2, a decrease in serum *p*H (acidosis) must be accompanied by a drop in carbon dioxide content. Similarly, an increase in serum *p*H (alkalosis) at constant alveolar pCO_2 must be accompanied by a rise in carbon dioxide content.

Carbon dioxide content is usually measured on venous blood samples kept under oil and stoppered to minimize loss of the gas (normal CO_2 content = 26–28 mEq./L.). To avoid hemolysis, the blood should be drawn gently through a large bore needle—yet, if tourniquets are used, it must be drawn rapidly to prevent stasis.

Carbon dioxide combining power. Serum may be equilibrated with carbon dioxide at a known partial pressure. The carbon dioxide content under these conditions is the carbon dioxide combining power. Since pCO_2 is known, and total CO_2 is measured, *p*H of the sample can be calculated (equation 7). With the pCO_2 controlled, respiratory factors would not be involved and this calculated *p*H would give some indication of physiologic acid-base changes independent of ventilatory contributions.

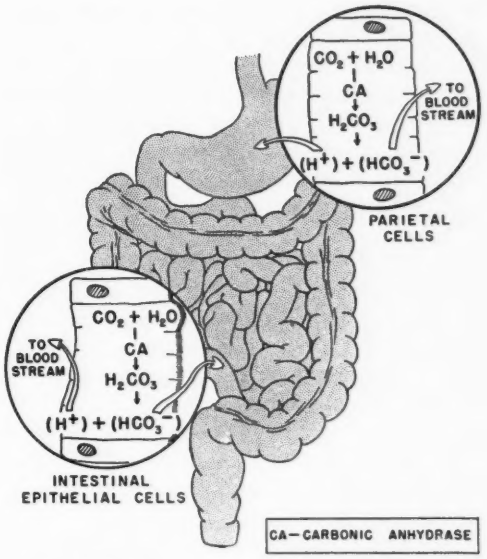

FIG. 3. The carbonic anhydrase system and gastrointestinal secretion.

In the clinical determination of carbon dioxide combining power, blood is not generally drawn under oil. Serum is separated from cells and, in most hospital laboratories, is equilibrated with a technician's alveolar air. The pCO_2 of this air is assumed to be 40 millimeters of mercury.

The difficulties in obtaining accurate or even reproducible pCO_2 values by this technique are considerable. When added to other inherent sources of error, such as equilibration of cell-free serum, the total error becomes so great that some hospitals have discontinued the use of carbon dioxide combining power in favor of measurements of *p*H and carbon dioxide content.

Hydrogen ion concentration. Hydrogen ion concentration is commonly measured on samples of venous blood drawn without stasis and kept stoppered under oil. A minimum of time should elapse between collection and measurement.

Use of the *p*H meter can give quite accurate values. Careful control of temperature and accurate standardization are most important here. Colorimetric methods, al-

though less accurate, are adequate for most purposes.

Equation (7) has three variables—*p*H, total CO_2 (CO_2 content), and pCO_2. Knowing any two of these variables permits calculation of the third. Nomograms have been prepared from the equation to facilitate such a calculation.

ACID-BASE REGULATION IN DISEASE

Although the Bronsted theory is valuable in the understanding of normal acid-base regulation, it is in cases of clinically deranged acid-base physiology that this theory seems to contribute greatest clarity and simplicity.

In the conditions discussed below, constant hydration and endocrine function are assumed.

Acidosis. Acidosis, by definition, is an increase in the hydrogen ion concentration of blood above normal, i.e., a decrease in blood *p*H below 7.4.

This hydrogen ion may come from several sources: (1) metabolic production of dissociated lactic, pyruvic, and beta-ketoacids in amounts exceeding the body's ability either to eliminate them or to compensate otherwise for them so as to maintain blood *p*H within normal limits; (2) dietary or parenteral intake of acids in excess of excretion or compensation; (3) retention of the acid normally produced; (4) abnormal retention of carbon dioxide with a resultant increase in circulating dissociated carbonic acid; (5) excessive loss of base.

Homeostatic compensation for acidosis is carried out primarily in the kidney and the lungs. The renal contribution to this homeostasis is merely an extension of the mechanism employed by that organ to excrete the excess of acid normally produced. This renal component is the same in all types of acidosis; bicarbonate is liberated into the bloodstream and an acid urine is excreted. The excess protons are excreted principally as the dihydrogen phosphate anion and the ammonium cation. The pulmonary factors in acidosis, however, vary with the type of acidosis and will be discussed in the following.

Metabolic acidosis. Metabolic acidosis, by definition, is an acidosis resulting from a relative excess of acid which is not freely excretable by the lungs. It is convenient to classify metabolic acidosis under three headings.

Acid-gaining acidosis.—Acid-gaining acidosis results from an increase in the absolute amount of blood acid. For example, when acid is administered orally or parenterally (HCl, NH_4Cl) or when excess acid is formed (keto acids in diabetes), there is an acid-gaining acidosis.

Base-losing acidosis.—In base-losing acidosis there is a net loss of blood base with a consequent *relative* excess of blood acid. Bicarbonate loss, as in intestinal diarrhea, biliary fistula, or vomiting of intestinal contents, will cause a base-losing acidosis.

Anuric acidosis.—Anuric acidosis is the acidosis resulting from the accumulation of normally produced acids in the face of renal shutdown.

Acid-gaining acidosis. Normally, in addition to the amino, phosphoric, sulfuric, and uric acids from protein and nucleic acid metabolism, the body produces acids in the course of carbohydrate metabolism (pyruvic, lactic, and succinic). Furthermore, fatty acids and short-chain hydroxyacids and keto acids are produced from the hydrolysis and breakdown of fats. In the normal, most of these acids are either metabolized to carbonic acid, and excreted by the lungs, or they are synthesized into cellular components—in which case the protons are generally neutralized.

There are conditions, however, in which these acids accumulate. For example, lactic acid accumulates in exercise, and beta-keto acids may accumulate in diabetes. When this occurs, or when acid production from protein metabolism is excessive, there is an acid-gaining acidosis and blood *p*H will be lowered. Similarly, when acids are administered orally or parenterally as, for example, hydrochloric acid or ammonium chloride,

the proton from the dissociation of the hydrochloric acid or the proton from the dissociation of the ammonium ion

$$NH_4^+ \rightleftharpoons NH_3 + H^+$$
$$\searrow$$
$$\text{UREA (Liver)}$$

produces a metabolic acidosis.

Renal compensation for a metabolic acidosis occurs primarily through bicarbonate formation and increased proton excretion; as we have seen, protons are excreted as ammonium and dihydrogen phosphate ions in an acid urine. In acid-gaining acidosis, excess anions are also excreted by the kidney. Thus, when hydrochloric acid is administered in large amounts, the excess chloride ion is eliminated. Similarly, anions of the keto acids formed in uncontrolled diabetes are eliminated in the urine. Urine *p*H does not drop below 4.5, thus the bulk of these anions such as acetoacetate (a typical keto acid anion) cannot be excreted associated with a proton. They form strong acids whose pK's are less than the *p*H of urine and hence only a small percentage is excreted in the protonated form (cf. equation 1). Since little hydrogen ion is lost with these anions, the *p*H of the blood is not appreciably raised by anion excretion alone.

Since excess anions must be eliminated in the dissociated form in prolonged, severe acid-gaining acidosis, there is a secondary increase in sodium excretion as electroneutrality of the urine is maintained. This sodium comes from plasma; hence, a decrease in serum sodium often accompanies a prolonged severe acid-gaining acidosis.[7] This sodium loss is secondary to anion excretion however, and is not primary in the regulation of blood *p*H.

Base-losing acidosis. A situation equally comprehensible in terms of the Bronsted theory occurs in intestinal diarrhea (e.g., Asiatic cholera, ulcerative colitis), or pancreatic fistula. It is probable that bicarbonate is secreted into the intestine from carbonic acid, formed with the aid of carbonic anhydrase. The carbonic acid dissociates with the liberation of hydrogen ion back into the blood, and the secretion of bicarbonate into the lumen of the gut (Fig. 3).

It follows then that if bicarbonate (base) is excreted in excess, as is the case in intestinal diarrhea, an acidosis must follow; the free hydrogen ion which is liberated into the bloodstream can no longer be neutralized by the bicarbonate that is lost. Sodium ion is excreted into the gut lumen along with the bicarbonate as electroneutrality of the intestinal juices is preserved. Hence, in intestinal diarrhea this sodium is also lost. As in acid-gaining acidosis, serum sodium is secondarily lowered, but in this base-losing acidosis, the sodium loss is extrarenal.

In this extrarenal base-losing acidosis, as indeed in any acidosis unaccompanied by an increase in renal anion excretion, there is an increase in renal proton excretion and a secondary decrease in urinary sodium excretion. Thus, renal sodium excretion may be increased in acid-gaining acidosis and decreased in base-losing acidosis, but the primary renal *p*H compensation—bicarbonate formation and proton excretion—is identical in both cases. The differences in sodium excretion between these two types of acidosis do not imply a different type of renal *p*H homeostasis. The renal acid-base compensations are the same; the differences in sodium metabolism are dictated by requirements of electroneutrality and are easily understood once the primary mechanism of regulation is clear.

Anuric acidosis. Anuria prevents the renal excretion of acids produced in the course of normal metabolism. In the case of acid-gaining acidosis or base-losing acidosis, serum sodium may fall.[8] In the anuric patient, however, there is no excretion of sodium by the kidney. In each case serum hydrogen ion concentration is high. Viewed in a Bronsted framework, the differences in sodium ion concentration need not confuse the fundamental pathologic physiology.

[7]Herein we have not considered alterations in endocrine function or hydration.

[8]The serum sodium level will rise or fall depending upon hydration, electrolyte shifts, and salt intake.

TABLE I.—ACIDOSIS—SODIUM SUMMARY TABLE

Type of acidosis	*Urine—sodium*	*Serum—sodium*
Respiratory	Decreased	Sl. increased
Acid-gaining	Increased	Decreased
Base-losing	Decreased	Decreased
Anuric	Decreased	Increased

Respiratory acidosis. Pure respiratory acidosis, by definition, occurs through an increase in pCO_2. As pCO_2 increases, more carbonic acid is formed. As this carbonic acid dissociates, the hydrogen ion liberated lowers blood *p*H—hence the acidosis. Such a mechanism is responsible for the acidosis seen clinically in the hypoventilation of emphysema, respiratory depression, and respiratory paralysis.

In respiratory acidosis, renal compensation proceeds through proton excretion, with concomitant liberation of bicarbonate, as it does in acidosis of any etiology. There is no increase in anion excretion; hence there is a decrease in the sodium excreted in the maintenance of electroneutrality. This decreased sodium excretion results in the slightly increased serum sodium concentration often seen in patients with a respiratory acidosis.

Changes in sodium ion concentration in the several types of acidosis, though important, need not be considered primary to an understanding of hydrogen ion regulation. In focusing on the hydrogen ion itself, both acid-base alterations and the concomitant electrolyte changes are more easily understood.

Clinically, patient response to a given acid or alkaline stress will be a function of several factors. Ultimate homeostatic regulation of an acid-base challenge will depend upon the buffering capacity of extracellular fluid, and perhaps intracellular factors, as well as upon the blood buffers. Thus, the quantitative adjustment of a patient depleted by persistent vomiting or diarrhea may differ from that of a patient whose reserves are adequate. It is beyond the scope of this paper to treat this problem of total body buffer. Likewise, the role of changing endocrine function and hydration cannot be considered here.

Acidosis and blood bicarbonate—carbon dioxide. If alveolar pCO_2 is maintained at the normal level, the Henderson-Hasselbalch equation permits appraisal of a metabolic acidosis in terms of the bicarbonate-carbonic acid system. An excess of hydrogen ion tends to convert blood bicarbonate to carbonic acid. Since pCO_2 remains constant in a pure metabolic acidosis, blood carbonic acid concentration remains constant. Excretion of the excess carbonic acid formed by the bicarbonate neutralization results in a decrease in blood bicarbonate without a decrease in blood carbonic acid. Looked at in another way (viz., equation 7), as *p*H decreases, total CO_2 decreases as pCO_2 remains constant. Since there are three variables in equation (7), knowing only two of the three (*p*H, total CO_2, pCO_2) enables calculation of the third and an instant appraisal of the total situation.

In actual practice, there is seldom a pure metabolic acidosis. Rather, the lungs as well as the kidneys, compensate to some degree and a metabolic acidosis is accompanied by some respiratory alkalosis. The summation of these processes results in a decreased pCO_2 with a smaller decrease in bicarbonate due to the respiratory component, and a marked decrease in bicarbonate concentration due to the metabolic component. Thus, as total CO_2 is markedly decreased, and as pCO_2 is compensatorily decreased (equation 7), there is a tendency for *p*H to stabilize (cf. Table I). The respiratory compensation for acidosis, if complete, would necessitate a considerable decline in pCO_2, but, in fact, both *p*H and pCO_2 are compromised, and the metabolic acidosis is generally only partially corrected by respiratory mechanisms.

Alkalosis. Alkalosis, by definition, is a decrease in blood hydrogen ion concentration, i.e., an increase in blood *p*H above normal. Alkalosis, like acidosis, may arise in several ways: (1) excessive dietary or parenteral intake of bases; (2) abnormal losses of acid from the gastrointestinal tract; (3) intra-extracellular shifts of hydrogen ion brought about by electrolyte or by hormonal abnor-

TABLE II

	pH	pCO_2	HCO_3^-	*Total* CO_2
Metabolic acidosis	Decreased		Decreased	Decreased
Respiratory alkalosis	Decreased	Decreased	Sl. decreased	Decreased
Net clinical result	Sl. decreased	Sl. decreased	Decreased	Decreased

malities; (4) abnormally great excretion of carbon dioxide by the lungs.

Renal compensation for alkalosis is achieved through conservation of hydrogen ion and excretion of base. Hydrogen ion is conserved by the cessation of ammonium ion excretion and the excretion of phosphorus as monohydrogen phosphate rather than the more highly protonated dihydrogen phosphate. Base is excreted as bicarbonate in a slightly alkaline urine.[9]

Since no ammonium cation is excreted, since the doubly negative monohydrogen phosphate anion predominates over the singly negative dihydrogen phosphate anion, and since bicarbonate, still another anion, is being excreted, urine sodium excretion is increased as electroneutrality is preserved. This sodium loss in alkalosis is an ancillary phenomenon dictated by the requirements of electroneutrality. When the primary acid-base phenomena are viewed in Bronsted terms the electrolyte changes are easily understood.

Metabolic alkalosis. Metabolic alkalosis, by definition, is an alkalosis resulting from an excess of blood base.

Bases taken orally or parenterally may be a primary cause of metabolic alkalosis. For example, when soluble, absorbable, bases such as sodium bicarbonate are given as antacids, the bicarbonate combines with protons of the gastric juice.

$$HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow H_2O + CO_2\uparrow$$

Thus hydrogen ion is lost to the body, or put another way, the basic bicarbonate secreted into the intestine is not now neutralized by protons from the stomach (Fig. 3). This unneutralized bicarbonate is reabsorbed into the blood from the intestine. Blood *p*H must rise in the face of this excess of bicarbonate (the numerator of the fractional term in equation 2 is disproportionately increased).

Insoluble, nonabsorbable bases (such as calcium carbonate or aluminum hydroxide) have only a minimal effect on blood *p*H. Although they dissolve in the acid gastric juices, combining with protons,

$$CaCO_3 + 2H^+ \rightarrow Ca^{++} + H_2CO_3 \rightarrow H_2O + CO_2\uparrow$$

$$Al(OH)_3 + 3H^+ \rightarrow Al^{+++} + 3\,H_2O$$

they reprecipitate in the alkaline (bicarbonate) medium of the intestine.

$$Ca^{++} + 2HCO_3^- \rightarrow (Ca(HCO_3)_2) \rightarrow CaCO_3\downarrow + CO_2 + H_2O$$

$$Al^{+++} + 3HCO_3^- \rightarrow (Al(HCO_3)_3) \rightarrow Al(OH)_3\downarrow + 3CO_2$$

They are not absorbed, and carry away from the intestine an amount of base equivalent to the amount added by them, and equivalent to the hydrogen ion neutralized by them in the stomach. Acid-base balance is thus essentially undisturbed (Fig. 3).

Sodium lactate as administered parenterally and potassium citrate or malate, as eaten in fruits, are themselves basic salts. Lactic and malic acids are highly but not completely dissociated at physiologic *p*H. The anions of malate and lactate, therefore, are weak bases, binding and neutralizing some of the hydrogen ion present in the blood. This results in a slight alkalosis.

e.g., $\underset{\text{(base)}}{\text{Malate}^-} + H^+ \rightleftharpoons \underset{\text{(acid)}}{\text{Monohydrogen malate}^-}$

The degree of alkalosis observed upon administration of such a basic salt will be initially dependent on the strength of the acid formed by the anion. The stronger the acid (the less hydrogen ion associated) the less the alkalosis produced. When these basic

[9] There is evidence that in severe alkalosis, tricarboxylic acid anions may be excreted in the urine. Their corresponding protons apparently are conserved and help compensate for the alkalosis.

anions are metabolized, moreover, the carbonic acid produced is excreted by the lungs but the bicarbonate formed remains as base, and further alkalosis develops.

$$\underset{\text{(lactate)}}{CH_3CH(OH)COO^-} + 3O_2 \rightarrow HCO_3^- + 2H_2CO_3 \xrightarrow{\text{lungs}} 2CO_2 + 2H_2O$$

It should be apparent that were acids such as lactic or citric themselves administered, the partial dissociation would increase the hydrogen ion concentration of the blood and cause an acidosis. These acids may be considered to be metabolized to carbon dioxide and bicarbonate as are their conjugate anions. In the case of the acids, however, the bicarbonate may be looked upon as associating with the proton of the acid, so that in effect, the acids are completely metabolized to carbonic acid and excreted in toto by the lungs.

$$\underset{\text{(lactic acid)}}{CH_3CH(OH)COOH} + 3O_2 \rightarrow HCO_3^- \cdot H^+ + 2H_2CO_3 \xrightarrow{\text{lungs}} 3CO_2 + 3H_2O$$

Thus, the effect of the acids, unlike that of their conjugate anions, is transitory. It is for this reason that in the treatment of an alkalosis the administration of an acid not ultimately excreted by the lungs is preferable. Ammonium ion (as NH_4Cl) is the acid most commonly used.[4]

There is convincing evidence that the protons of gastric juice are secreted into the stomach lumen from dissociated carbonic acid. The carbonic acid is formed with the aid of carbonic anhydrase in the parietal cells, and the bicarbonate formed as protons are secreted passes into the blood. This results initially in a slight alkalosis ("alkaline tide") until this bicarbonate is neutralized by protons formed in the secretion of alkaline intestinal juice (or until the hydrogen ions are reabsorbed).

If the protons in the stomach are lost, as in the vomiting of gastric contents alone (e.g., in pyloric stenosis), there will be a net excess of bicarbonate over hydrogen ions passing into the blood from the gastrointestinal tract, and an alkalosis. Associated with this alkalosis is a low serum chloride, ("hypochloremic alkalosis") since chloride ion as well as hydrogen ion is lost in the vomitus. Chloride loss in itself is not a primary factor in producing the *p*H alteration, however.

Alkalosis accompanying potassium deficiency has been attributed to a shift of hydrogen ion from the bloodstream into the cells. Such a proton shift may account for the alkalosis seen clinically in hyperadrenocorticism, as well as that seen in primary hypokalemia. In addition, potassium deficiency may result in an increased proton excretion, since a reciprocal relationship between potassium ion and hydrogen ion secretion seems to exist in the renal tubule.[10] This mechanism is consistent with the finding of an acid urine, despite the presence of systemic alkalosis, when hypokalemia is the cause.

The foregoing discussion of alkalosis in potassium deficiency assumes that it is the loss of potassium which produces extracellular alkalosis in man. This is an attractive hypothesis, but it is well established that metabolic alkalosis itself (as seen with the loss of protons through vomiting of gastric hydrochloric acid) can lower the plasma potassium concentration (hypokalemia), regardless of external balance.

Although basic mechanisms are not completely understood, the Bronsted theory permits a clear statement of phenomena for which good evidence exists:

1. Loss of protons (alkalosis) lowers the serum potassium concentration.

2. Gain of protons (acid-gaining acidosis, as in renal disease) raises the potassium concentration of serum.

3. The loss of potassium from the body may not alter the potassium concentration of serum. In certain circumstances potas-

[10] A possible compensatory excretion of basic tricarboxylate anions may be defective in the potassium-deficient animal. Moreover, in such animals, ammonium ion excretion and bicarbonate resorption seem to be increased, thereby heightening the alkalosis already present.

sium loss may produce a shift of protons into the cell with the production of extracellular alkalosis; with this there occurs an alteration in renal tubular function characterized by the secretion of an acid urine and the increased resorption of bicarbonate.

4. The physiologic derangements can be corrected by administration of potassium; acids such as ammonium chloride have less effect.

Respiratory alkalosis. Pure respiratory alkalosis, by definition, occurs through a decrease in pCO_2. As pCO_2 decreases, carbonic acid is eliminated, and blood *p*H rises. Hydrogen ion concentration falls as protons are associated with bicarbonate:

$$H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$$

This increased excretion of carbonic acid is responsible for the alkalosis seen clinically with the hyperventilation of hysteria.

Alkalosis and blood bicarbonate—carbon dioxide. With pure metabolic alkalosis, the pCO_2 remains constant. The increase in base neutralizes the hydrogen ion from carbonic acid dissociation, shifting the equilibrium to increase the bicarbonate concentration. Thus, bicarbonate and total CO_2 are both increased, at a constant pCO_2, when the *p*H is raised in metabolic alkalosis.

As in metabolic acidosis, one would expect some respiratory compensation for metabolic alkalosis.[11] A partially compensating respiratory acidosis should increase pCO_2 and increase bicarbonate concentration somewhat less. The resultant compromise would still leave a *p*H somewhat above normal, a bicarbonate concentration higher than normal, an elevated total carbon dioxide concentration, and a pCO_2 slightly above normal (Table III). If the alkaline blood is saturated with carbon dioxide at a controlled pressure, the total carbon dioxide (CO_2 combining power) is increased; this is due primarily to the increase in bicarbonate formation as the carbonic acid dissociation is favored.

[11]Recent experiments in H. T. Randall's laboratory suggest that this expected respiratory compensation may not actually occur.

TABLE III

	Total CO_2	pCO_2	HCO_3^-
Metabolic alkalosis	Increased		Increased
Respiratory acidosis	Increased	Increased	Sl. increased
Net clinical result	Increased	Sl. increased	Increased

Renal mechanisms for the compensation of alkalosis have already been discussed. Protons are conserved as no ammonium ion is excreted and as phosphate is excreted as the monohydrogen anion rather than the more highly protonated dihydrogen phosphate. Base is excreted in the form of bicarbonate and perhaps tricarboxylates in a slightly alkaline urine and the blood *p*H is consequently lowered.

SUMMARY

According to the Bronsted theory, an acid is a hydrogen ion donor and a base a hydrogen ion acceptor. In this simple framework, mechanisms of normal and deranged acid-base physiology have been sketched. Renal function in acid-base balance has been considered and the role of carbonic anhydrase in proton excretion has been emphasized. Carbon dioxide transport has also been examined; the role of hemoglobin in this process, and the concomitant electrolyte shifts are easily understood in terms of the Bronsted theory.

It is in the realm of clinically deranged acid-base balance, however, that the Bronsted theory appears most valuable. A number of pathologic conditions have been discussed, and, in all, this theory seems to lend clarity and simplicity.

In acidosis, blood hydrogen ion concentration falls. Renal compensation for this increase in hydrogen ion is by liberation of bicarbonate into the blood with concomitant excretion of protons—as ammonium ions and as dihydrogen phosphate ions—in an acid urine. This proton excretion mechanism occurs, whether renal sodium ion excretion is increased, as in acid-gaining acidosis, or decreased, as in respiratory, or in base-losing acidosis. This mechanism applies whether serum sodium is decreased, as in acid-gaining acidosis and base-losing aci-

dosis or increased, as may occur in respiratory acidosis.

In alkalosis, the normal kidney conserves acid by failing to excrete ammonium ion and by excreting monohydrogen phosphate rather than forming the more highly protonated dihydrogen phosphate. The kidney can also excrete base as bicarbonate and possibly tricarboxylates. Renal compensation for alkalosis is thus simply conservation of acid and excretion of base.

The unity inherent in the Bronsted theory seems to afford a simple and precise presentation of the mechanisms of acid-base balance. Once the primary hydrogen ion regulation is understood, the electrolyte alterations become apparent from the requirements of electroneutrality.

EDITORIALS

A NATIONAL MEDICAL LIBRARY

I. S. RAVDIN, M.D., F.A.C.S., Philadelphia, Pennsylvania

THE ARMED FORCES MEDICAL LIBRARY is one of the finest in the world, if not the finest. It contains approximately a million books and pamphlets, and in it can be found nearly every medical journal published in the world. It has traditionally supplied medical information to every institution that has requested it.

For many years it has not only been inadequately housed, but it has been shabbily supported. It was originally known as the Army Medical Library. Mr. Louis Johnson, when Secretary of Defense, came to the opinion that the cost of maintenance of the Library was not a just charge against the Department of Defense. The Division of Medical Sciences of the National Research Council was requested to appoint a Committee to study this entire problem. It came into being at a time when General Marshall was Secretary of Defense. He expressed the opinion that he would be guided by what the Committee, appointed by the National Research Council, recommended.

It had been suggested at about this time that the Armed Forces Medical Library be turned over to the Smithsonian Institute or to the Library of Congress. The Committee of the National Research Council did not agree with this opinion. They believed not only that the Library should be housed adequately but that it should be financed generously. It is an indispensable aid to medical research and medical progress.

Although General Marshall accepted the report of the Committee, the Department of Defense has never encouraged legislation to provide for the Library by a new building or by additional financial support: this, in spite of the fact that Major General George E. Armstrong, then the Surgeon General, recommended that the Library be moved from its present location to the United States National Naval Hospital at Bethesda and be directed alternately by representative medical officers of the Army, Navy, and Air Force. Senators Lister Hill, and John F. Kennedy, have introduced a Bill (S.3430) the title of which is "To Promote the Progress of Medicine and to Advance the National Health and Welfare by Creating a National Library of Medicine." The Bill recommends that there should be a Board of Regents "composed of the Surgeons General of the Army, Navy, Air Force, and Public Health Service, and the Librarian of Congress, who shall be ex officio members, and twelve individuals appointed by the President by and with the advice and consent of the Senate and without regard to political affiliation." The Bill further authorizes the Board of Regents and, in fact, directs them, "to have prepared drawings and specifications for, and to construct, a suitable building or buildings for the use of the National Library of Medicine, in a location suitable for the purpose of enabling persons most concerned with the health affairs of the Nation to have ready access thereto."

The building which now houses the Library is 69 years old, and it has been considered inadequate for more than 30 years.

On four occasions since 1919, Congress has authorized the Military Establishment to draft plans for a new building. Nothing has come of this. The Library is now 120 years old. A Medical Task Force of the Commission on Organization of the Executive Branch of the Government stated speaking of the Armed Forces Medical Library that "no other Government Medical Agency serves the future of medical research so intimately and so widely" as does this great Library.

It has been reported that the Defense Department, which originally opposed the Bill, is ready to withdraw its objections.

I have followed the tides of fortune relating to the Armed Forces Medical Library during the past decade. There can be no question but that new physical facilities are urgently needed. It has been stated that an extra mile of shelf space is needed each year.

Although the Library houses a priceless collection, it is housed in a building which is, in reality, a firetrap. The splendid items of medical antiquity may well be destroyed unless adequate facilities for housing them are made possible in the very near future.

The Bill introduced by Senators Hill and Kennedy has been endorsed by nearly every professional organization which is concerned with health. The American Medical Association, The American Dental Association, The American Hospital Association, and The American College of Surgeons thoroughly endorse this Bill. This great Library, newly housed and adequately supported, as contemplated in the Bill, will do much to further research in many fields of effort. It is a short-sighted policy to provide funds for research without providing funds for a National Medical Library which the research worker must constantly use.

PROBLEMS IN HEMORRHOIDAL DISEASE

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STUDIES OF THE CAUSATION of hemorrhoidal disease are still inconclusive. Absence of valves within the hemorrhoidal veins and lack of substantial support of the venous plexus in the submucosa of the rectum constitute substantial anatomic handicaps that may be responsible for the reverse flow of the venous blood; these handicaps may be aggravated by the factor of gravity favoring stasis in the vascular tree and resultant passive congestion. A familial tendency toward the formation of hemorrhoidal varices is quite conspicuous in many patients. I have treated hemorrhoidal disease in 3 generations of the same families on numerous occasions. Infection of the anal structures, including perivascular inflammation, is of dubious etiologic consequence as is the suggestion that hemorrhoids are a collagen disorder. Occupational strain may be of importance in precipitating prolapse of existing internal hemorrhoids (as well as in the production of perianal hematomas).

The management of hemorrhoids offers three alternatives: They may be neglected, injected, or resected. In my experience, over 20 per cent of patients with anatomic hemorrhoids discovered either by the patient or by the physician in the course of a routine physical examination are either asymptomatic or so mildly symptomatic that no therapy is indicated. Another 30 per cent of the patients are suitable for injectional sclerosing therapy. They have small to medium-sized internal, usually bleeding, prolapsing but spontaneously reducible piles. Still another 40 per cent of patients who have either large internal or internoexternal (mixed) hemorrhoids with or without bleeding, pain, or protrusion require surgery. The remaining 10 per cent of patients constitute the border-line cases or those with concomitant systemic disease in whom a trial of conservative therapy is justified. However, a personal study of patients with systemic disease on whom I eventually have performed hemorrhoidectomies following a trial of injectional sclerosing therapy has convinced me (as well as the patients) of the superiority of surgery in the presence of clear-cut local indications.

For patients with strangulated internal hemorrhoids, I prefer immediate hemorrhoidectomy to conservative management or watchful waiting. In such instances delay may allow marked swelling of the external components and spasm of the anal sphincter muscles which obscure anatomic landmarks rendering surgery difficult. Prompt operation eliminates protracted pain and makes possible early economic rehabilitation.

Hemorrhoids should never be accepted as the cause of gastrointestinal bleeding until complete proctologic and general physical examinations (to exclude causative systemic disease) have been performed. All patients with overt or occult rectal bleeding, regardless of age, should have sigmoidoscopic and radiographic examinations to exclude the presence of an adenoma or cancer. Likewise, a complete blood count is mandatory to recognize blood dyscrasias which are frequent causes of rectal bleeding, and to judge how much anemia is present as a result of blood loss. Patients with unexplained iron deficiency anemias should be accorded a proctoscopic survey to determine whether unsuspected internal hemorrhoids (and other lesions such as adenoma or cancer) are the source of the slow or chronic blood loss which, when accompanied by a blood volume deficit, may create a clinical picture resembling organic heart disease.

The large number of techniques of hemorrhoidectomy described in the literature indicates dissatisfaction with the operation by

many surgeons. My contact with surgeons from different parts of the United States during World War II has convinced me that the open nontraumatizing technique is the most successful operation in the hands of the average surgeon. In this procedure, the pathologic tissue is removed widely but sufficient elastic integument and mucosa between wounds are preserved; blind or mass clamping and bulk ligation are avoided. This technique is based on the principles first enunciated by Hippocrates which still form the basis of all modern techniques of hemorrhoidectomy.

Following the performance of this technique of hemorrhoidectomy, the pain is minimal and may be easily controlled by narcotic or derivatives of the coal tar drugs; there is no need for the employment of either the long-lasting anesthetic solutions, including efocaine, or d-tubocurarine in oil (tubadil). Besides failing to control pain effectively in many instances, the anesthetic drugs like other caustic agents, such as phenol or alcohol, cause neurolysis and may produce untoward reactions such as serious necrosis, suppuration, or incontinence in some cases. Curare, by producing general muscular relaxation and impairment of muscle control, interferes with early ambulation of the patient and adds new problems to the already overburdened and critically short trained nursing personnel. These calculated risks are decidedly unjustified. The discreet surgeon avoids the use of these drugs as the severity of the pain does not depend on the use or nonuse of these agents. Furthermore, these drugs are poor substitutes for refinements of technique or gentleness in handling tissues during operation; at best these agents are therapeutic crutches fostering a false sense of security and dependence on a drug.

My recent studies have disclosed that the conventional periodic digital explorations or examinations, or the special topical application of medications such as vitamins, chlorophyll, and so forth, to anorectal wounds following the open technique of hemorrhoidectomy failed to influence or expedite the healing process of the wounds; the controls in whom the postoperative wounds were left practically undisturbed healed just as effectively. These maneuvers are performed regularly either as a result of custom, habit, and tradition, or their use is dictated by the dire need resulting from a poorly conceived technique or a poorly executed initial orthodox hemorrhoidectomy.

Primary closure of anorectal wounds, even with the preoperative and postoperative employment of sulfonamide or antibiotic agents, still carries a prohibitive incidence of wound complications. It is of questionable value even in military practice where the saving of days of effective healing is so important during war time.

Recurrence of hemorrhoids following a well performed hemorrhoidectomy may be the result of incomplete removal of the primary varices which is preventable, or the inevitable result of the enlargement with the passage of time of the secondary hemorrhoidal varices that were inconspicuous at the time of the original operation. I believe that the latter cause comes into play oftener than is usually appreciated; lack of proof for this contention at the time of the present writing is no proof of its absence.

THE SURGEON AT WORK

UTILIZATION OF EXCESS SKIN TO GRAFT DEFECTS FOLLOWING RADICAL MASTECTOMY

LOUIS R. SLATTERY, M.D., F.A.C.S., New York, New York

SPLIT THICKNESS SKIN GRAFTS are usually used to surface the skin defect resulting from a radical mastectomy. This procedure necessitates a second operative wound on some other portion of the body as well as the use of specialized instruments. The procedure to be described avoids these disadvantages as it utilizes the loose excess skin of the wound flaps which otherwise serves no purpose and may be a focus for a collection of serum postoperatively.

The skin defect after radical mastectomy occurs in the central portion of the incision. Elsewhere, there is an excess amount of skin resulting from the collapse of the soft parts of the chest wall secondary to removal of the pectoral muscles. The superior portion of this excess skin falls in to cover the dissected axilla while the inferior portion remains loosely attached to the chest wall after approximation of the wound edges. Because of the availability of this skin, the local excess has been excised and used as a free full thickness graft after removal of the subcutaneous fat and areolar tissue. When the Halsted-Meyer incision is used the graft is obtained from the inferior portion of the lateral flap while with the Stewart incision the graft may be obtained from the lateral extremity of the inferior skin flap. Adequate amounts of skin are available from these sites to cover all except the massive defects encountered after palliative procedures for advanced cancer.

A full thickness graft applied to a clean surface such as a mastectomy defect seems to take as readily as a split graft. Furthermore, a full thickness graft provides a more satisfactory covering for the thorax than a split graft.

Review of the literature reveals no previous use of this method to surface skin defects after radical mastectomy.

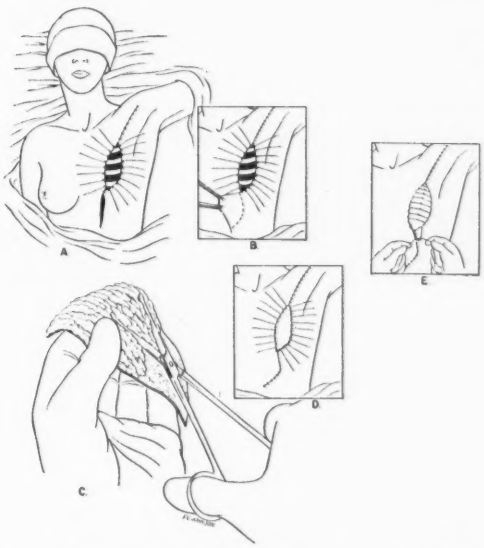

FIG. 1. A, The upper portion of the incision has been closed and 1 suture placed at the lower extremity of the skin defect. The margins of the defect have been anchored to the chest wall and the ends of the sutures left long. B, Loose skin of lateral flap is placed on stretch and line of excision noted so that graft of adequate size is obtained without removal of too much skin from flap. C, Fat and areolar tissue are removed from excised skin. D, Graft is sutured in place and remainder of incision closed. E, Gauze stent is tied over graft.

From the Department of Surgery, New York University Post-Graduate Medical School, New York.

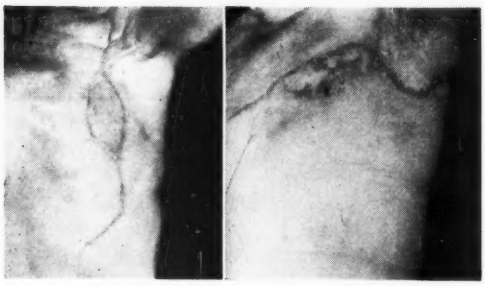

FIG. 2. FIG. 3.

FIG. 2. Defect grafted after Halsted-Meyer incision.
FIG. 3. Defect grafted after Stewart incision.

TECHNIQUE

After removal of the operative specimen and ligation of all bleeding vessels, the closure of the incision is begun superiorly in vertical incisions and medially in transverse incisions. When it becomes obvious that the central portion of the incision cannot be approximated, the inferior margin of the defect is approximated with 1 suture (Fig. 1A), or in a transverse incision the lateral extremity of the defect is approximated with 1 suture. The margins of the defect are then anchored to the chest wall with interrupted cotton sutures (Fig. 1A) the ends of which are left long for subsequent fixation of the graft with a gauze stent. The subcutaneous fat of the inferior portion of the lateral flap (Fig. 1B) is grasped with 2 Allis forceps and placed on sufficient stretch to remove an ellipse of skin approximately the size of the defect. At the same time the surgeon is able to see that sufficient skin is left to permit closure of this portion of the incision. With a transverse incision an ellipse is similarly removed from the lateral portion of the inferior flap. After removal of the fat and areolar tissue (Fig. 1C) the graft is applied to the defect and approximated to its margins with interrupted cotton sutures. A pad of gauze 2 centimeters thick cut in the shape of the defect is applied to the graft as a stent, and the sutures previously left long are tied over it to maintain fixation and even apposition to the thoracic wall. The remainder of the operative incision is then closed. Suction drainage of the axillary portion of the operative area by Raffl's[1] method has been used while no drains have been necessary in the inferior portion of the operative area where removal of the graft effects a tight application of the skin to the chest.

CONCLUSIONS

A method has been described of correcting defects resulting from radical mastectomy by the use of full thickness grafts from the excess skin at the wound margins. This procedure obviates a second operative wound and requires no special equipment. The skin so applied forms a better covering for the rib cage than a split thickness graft.

[1]RAFFL, A. B. The use of negative pressure under skin flaps after radical mastectomy. Ann. Surg., 1952, 136: 1048.

THE SURGEON'S LIBRARY

Reviews of New Books

THE WELL ORGANIZED and comprehensive volume, *Chirurgie de la main*,[1] consists of two main parts: the first and larger part, of approximately 600 pages, includes a major section of 450 pages devoted to the sequelae of injury and a second section of 150 pages devoted to acquired lesions which includes also a discussion of congenital deformities. The second part of the volume, 350 pages, is a reprinting of an earlier work of the author (1946) in which he considers open and closed injuries of the hand and their immediate treatment, and infections of the hand.

The first 450 pages of the volume are divided into 10 chapters in which the author considers in turn the diagnosis of injuries (Chapter I), and general considerations of treatment (Chapter II), with particular reference to various methods of splinting and to physical therapy. In succeeding chapters (III to X), the author discusses in turn: injuries involving skin and subcutaneous tissue—contractures, burns, radiation injuries; bone injuries; joint injuries; injuries of tendons; nerve injuries; amputations and their sequelae; reformation of the thumb and fingers; and replacement of the amputated hand.

These chapters are exceedingly well written and reflect not only the author's wide experience, but also his extensive study of and acquaintance with the work of American and other European surgeons.

Of particular interest to the author is the problem of tendon repair, both from the standpoint of surgical treatment and of postoperative care. He accepts, for the most part, the teachings of Bunnell and favors the use of metallic sutures because of the absence of reaction about them. Concerning his attitude toward the problem of aftercare following tendon operations he leaves the reader in some doubt. He says (p. 224) "Until 1935 I mobilized (the digits) early; from 1935 to 1945 I mobilized (them) late, with improvement in the results. In 1947 and 1948, after some conversations with Pulvertaft I returned to early mobilization, without observing any particular improvement; (the results were) no better, no worse."

The problem of reconstruction of the thumb and fingers has interested the author greatly, and is discussed at considerable length in a well illustrated chapter (IX) of 50 pages.

The section on acquired deformities (Chapters XI to XVI) includes chapters on: Dupuytren's contraction (XI); chronic tenosynovitis (XII); arthritic deformities (XIII); tumors (XIV); and congenital malformations (XV and XVI). These chapters are very well illustrated, and the methods advocated in the treatment of the conditions discussed are almost uniformly in accord with what American workers in this field consider good surgical practice. In the treatment of finger contractures associated with Dupuytren's contraction the author describes and illustrates the use of the Z-plasty, a method which would seem indicated only in the occasional case, since the thick palmar skin, often almost rigid along the line of contracture, does not lend itself to plastic procedures. If he uses a skin graft the author prefers to apply it from 5 to 7 days after operation rather than immediately, in the belief that there is no risk of hematoma formation and that the granulation tissue which has covered any exposed nerves provides an even surface for the application of a "skin dressing" and one which does not require sutures.

Throughout this entire volume there is every evidence of the author's continuing interest in the many problems involved in the surgery of the hand and of his persistent efforts to raise the standards of treatment of the many patients, both in military and civilian life, for whom injuries and disabling affections of the hand constitute so serious a handicap. —*Sumner L. Koch.*

THE SECOND EDITION of Warren Cole's *Operative Technic in General Surgery*[2] is a very splendid successor to the popular first edition published in 1949.

The present volume with 67 contributing authors has been very extensively revised and numerous new illustrations have been added. Three new chapters are included in this volume covering "Blood Transfusions and Allied Problems," "Gastrointestinal Surgery in Infancy and Childhood," and "The Appendix." To make room for these additions 3 chapters formerly included in Volume I have been transferred to Volume II, yet to be published.

In the Foreword to the original volume the late Frank Lahey said this work had the great advantage of having the various subjects presented by men who have had particular experience with the subject about which they wrote. This advantage persists in the second

[1] CHIRURGIE DE LA MAIN. By Marc Iselin. Livre du chirurgie. 2nd rev. ed. 626 pages, 319 illustrations. 4.000 fr. Paris: Masson & Co., 1955.

[2] OPERATIVE TECHNIC IN GENERAL SURGERY. Edited by Warren H. Cole, M.D., F.A.C.S. With 67 Contributing Authors. 2nd ed. Introduction by Frank H. Lahey. 973 pages, 1247 illustrations. $20.00. New York: Appleton-Century-Crofts, Inc., 1955.

edition, since essentially the same authors have served as contributors excepting when new subjects have been included.

It is noteworthy to see the great advances that have been achieved in nearly all subjects in the 6 years between editions. One is especially impressed with the technical advances in surgery of the esophagus, pancreas, breast, and in pediatric surgery when the 2 volumes are compared and a large mass of concentrated material reviewed.

This is a very readable volume as was its predecessor and will be found a useful companion for the mature surgeon and of tremendous value for the younger men in training. —*C. W. McLaughlin, Jr.*

THE 56 PAGE MONOGRAPH entitled *Hypothermic Anesthesia*[3] is a clear and well organized digest of what is known about hypothermia. Early observations on animals and human beings are recounted. Then follows the recent observations of the physiologic effects of hypothermia in animals, and the techniques suggested by the various workers in this field. There is a discussion of ventricular fibrillation, a frequent consequence of cooling. Chapters are devoted to clinical experiences, complications, and an outline of the author's procedure.

Finally, there is a discussion of the several factors that need further elucidation and research work. The reader emerges at the end with the realization that though much is understood about hypothermia, much more is controversial. To quote the author: "This essay should not be considered a summary on hypothermia anesthesia, but should be taken as an interim report on its status." —*Mary Karp.*

THE BOOK entitled *Peripheral Vascular Disease*[4] by Barnett and Fraser is based on the prize-winning essay for the Stawell Memorial Prize of the British Medical Association (Victorian Branch) for 1952. It is a small volume of 219 pages which briefly covers most of the conditions in the field from the medical point of view. After a short historical review there is an excellent chapter dealing with the physiology and mechanics of peripheral circulation. This is followed by a discussion of the various diagnostic methods and then a fine chapter on the pathologic changes found in the conditions discussed in the book.

The clinical features of the different diseases are well illustrated by numerous brief, case reports. The various treatments used are described and the authors discuss their own results with each method critically. The newer surgical procedures are mentioned very briefly and the techniques are not described.

This volume should be a worth while addition to the surgeon's library. —*Samuel Perlow.*

THE VOLUME entitled *Atlas of General Surgery*[5] by Wilder is similar to but not as detailed as the *Atlas of Surgical Operations* by Cutler and Zollinger, published in 1939 and revised in 1949. It has the same general defects which were so well pointed out by Dr. Coller in his review of Cutler and Zollinger's Atlas, in 1940 (*Surg. Gyn. Obst.*, 1940, 71: 533). "The folio size of the book makes it a mechanical nuisance in any modern library. Since the work is after all a skeleton, it is to be hoped that it will be used only by those young surgeons whose training gives them succulent tissue of physiology, chemistry, and pathology to cover the dry bones thus presented. For one whose training does not offer this scientific padding, one can only hope that they will realize that pictures do not bleed and that large folio volumes do not die of pneumonia, of embolism and of shock."

In a day when surgical principles and techniques are stressed in well conducted surgical training programs one wonders to what purpose this book is written. The author hopes "it will serve as a reference for students, interns, residents, and practicing surgeons seeking guidance in operative procedures." Much of the subject matter would be confusing to students and possibly to interns as well who have little time and energy enough to learn the more fundamental principles relating to medicine. To residents who are well along in their training program or practicing surgeons who have already established technical know-how, the book may serve to make them more satisfied with their own techniques.

The reviewer is struck with the great similarity to Cutler and Zollinger. It has one advantage in that it is published on better paper, with illustrations which, while containing less information, are easier to look at. The sections on preoperative considerations and surgical techniques in the operating room are so sketchy, so trite, and reflect so much the author's own preferences as to be of little use. In general, the "Important Considerations" which accompany each section could in most instances have been left out, thereby decreasing the size of the book. Most of the "Important Considerations" listed are true for all operations and could have been assumed or described once instead of being repeated, since sterile technique seems standard enough as do hemostasis, avoidance of injury to important structures, and control of infection. Frequent reference to meticulous dissection and meticulous hemostasis, suggests that the surgeon must approach each operation with care born of fear rather than a knowledge of principles.

Most of the illustrations and their descriptions follow generally accepted patterns and with variations are followed by most surgeons. It is the necessary variatons from standard, however, which makes good surgical training necessary with more detailed study of surgical literature. The details of the operations present but one way of doing them, and no two surgeons are likely to agree on all details.

For a casual perusal of the illustrations this book will be enjoyable in spite of its awkward size. For the surgical resident who recognizes the limitations of the illustrations, this book might afford a generalization of the operation at hand, and encourage him to seek sources of information which give a more vital and basic concept of the operative procedure.

—*Charles G. Johnston.*

[3]HYPOTHERMIC ANESTHESIA. By Robert W. Virtue, M.D., Ph.D. 62 pages, 2 illustrations. $2.50. Springfield, Ill.: Charles C Thomas, 1955.

[4]PERIPHERAL VASCULAR DISEASE. By A. J. Barnett, M.D., M.R.C.P.(Lond.), M.R.A.C.P., and J. R. E. Fraser, M.D., M.R.A.C.P. 219 pages, 31 illustrations, 39 plates. $9.50. Australia: Melbourne University Press; New York: Cambridge University Press, 1955.

[5]ATLAS OF GENERAL SURGERY. By Joseph R. Wilder, M.D. 222 pages, 101 plates. St. Louis: The C. V. Mosby Co., 1955.

THE FIFTH REVISION of the textbook entitled *The Surgical Technic of Abdominal Operations*,[6] which was published for the first time 20 years ago, is divided into 5 parts and 27 chapters. The subject matter is admittedly compiled for the study of the fundamental techniques of abdominal operations, as presented to undergraduate students and poorly informed graduate students. There is unquestioned good in the book. It exists in narrative form, which is amply augmented by illustrative sketches, most of which are excellent.

The arrangement of the material is not necessarily one of progression from simple abdominal procedures to the most difficult. The narrations appear in a simple form and are probably as clearly presented as any word descriptions of these technical procedures can be. The form of the book is a forerunner of the more popular "atlas books" and is obviously an attempt to combine the narrative and pictorial media for pedagogical edification. Each section contains documented remarks about the historical development of the subject about to be presented, with doubtful accuracy at times, but with the allotment of too much space when the subject matter is stated to be technique of operations. The historical facts may well benefit a lecturer or teacher who wishes to present developments of certain surgical procedures.

The bibliography contains a definite continental flavor, which is certainly correct for the earlier operations, many of which are now obsolete. It is by no means a complete bibliography, but could be useful as a guide to other important and particularly recent contributions on the subject matter at hand.

It is inconceivable to presume that the embryonic abdominal surgeon could profit by reading Chapter 1, which is devoted to descriptions of sutures, knot-tying, ligatures and basic suturing, and stitches. The novice simply does not perform or study abdominal operations as his first effort in surgery.

The new chapter on "Peritoneal Cavity, Peritoneal Folds, Ligaments and Fossae" is interesting and worth while.

The section on "Gastrostomy" describes so many procedures that the student must be hopelessly confused by it. One wonders why the author has not chosen a few commonly-used procedures for illustration instead of 11 procedures.

The sections on "Gastropexy" and "Hepatopexy" should definitely be omitted. Modern surgical literature does not substantiate any good that might come from their use.

The sections on the "Stomach, Pancreas, and Spleen" are not up-to-date, but contain many well-known facts and are valuable. Some incorrect and dangerous methods are advocated. For instance, after quoting Lehman, who recommends duodenojejunostomy for annular pancreas, the author advocates resection of the pancreatic ring; also, vitallium tubes are no longer considered to be of good usage in blood vessel anastomoses. Much space is wasted on several methods for splenopexy, which is an ancient and now obsolete operation. The type of ileostomy described in its appropriate chapter is indeed a poor one at best, and the waiting period of 6 to 12 months before surgical correction of fecal fistulas can be dangerous as well as time-consuming.

The chapter on "Gallbladder Surgery" would be excellent if a few ancient reminders were not described to add to the confusion of the student reader.

The chapter on "Malformations of the Intestinal Tract" is one of the best in the book, although far from complete.

"Vagotomy and Cardiospasm" receive some consideration—perhaps as much as they deserve. The customary approaches and commonly used procedures are described.

In a greatly simplified form and in a practical manner, the subject of hernia is presented, although none of the newer anatomic niceties or prostheses are discussed. Chronologically, this section may well have been Chapter 1, if a textbook should proceed from simple things to more complex things.

The short chapter on "Abdominal Gynecology" is useful, decidedly not profound, and contains the poorest illustrations in the book. It is far from complete. Some of the space assigned to obsolete procedures in the earlier sections may well be used for embellishment of a better understanding of gynecologic abdominal procedures. This section could be extremely useful to the abdominal surgeon who must also perform gynecologic operations.

This textbook appears to be a book written about the year 1930, by an author who is permitted slight telescopic views of the surgical world in 1956, but enough is not seen to pull the manuscript away from the antiquated surgical doings of ancient days.

—*Ralph F. Bowers.*

THE VOLUME entitled *Atlas of Bronchial Lesions in Pulmonary Tuberculosis*[7] is a beautiful book and full of valuable information. It is based entirely on a study of surgically resected specimens from the Kloggenberg sanatorium in Breda at which Dr. Dijkstra is the medical superintendent. This institution is one of the largest tuberculosis sanatoria in the Netherlands. The subject matter is not solely concerned with the pathologic findings, but is a presentation of the subject with complete details as to the history, bacteriologic findings, x-rays, and bronchograms. The photographs of the specimens are excellent with views of the gross specimen and photomicrographs of involved bronchi.

The author points out that in the past there has been no comprehensive survey of bronchial changes in tuberculosis, and he, therefore, reviews the incidence and nature of bronchial changes. He also discusses the pathogenesis of bronchial tuberculosis from the data presented. He believes that all changes observed in the bronchi in pulmonary tuberculosis are of a specific tuberculous nature, and that secondary micro-organisms play no important role from the clinical standpoint. He also agrees with Auerbach that secondary infections play no part whatever in the pathogenesis of cavitary lesions.

[6] THE SURGICAL TECHNIC OF ABDOMINAL OPERATIONS. By Julius L. Spivack, M.D., LL.D., F.A.C.S. 5th ed. 931 pages, 1037 illustrations on 495 figures. $17.50. Springfield, Ill.: Charles C Thomas, 1955.

[7] ATLAS OF BRONCHIAL LESIONS IN PULMONARY TUBERCULOSIS; A CLINICAL AND MORBID-ANATOMICAL STUDY. By C. Dijkstra, M.D. 128 pages, 131 illustrations. $11.00. Springfield, Ill.: Charles C Thomas, 1955.

The material in the book is divided into two main groups. In consideration of the first he discusses the changes in the bronchi in primary and postprimary tuberculous obstructive lesions, and in obstructive infiltrations of phthisic origin. With the other group he considers the bronchial changes found in other forms of tuberculosis. This group is subdivided into the cases with changes in the bronchi which drain cavities and major caseous lesions or tuberculomas; and the cases with bronchial changes in atelectatic, fibrocirrhotic, and indurative lesions.

This is an all inclusive study and will prove to be of great value for reference as well as a most interesting book to read and study.

This volume is such an excellent one that few flaws can be found in it. There are two defects which should be mentioned. The first is the omission of roentgenograms and data as to surgery in the section dealing with changes of the bronchi in phthisic forms of tuberculosis. The other has to do with some of the bronchograms which have been reproduced. A number of these fail to demonstrate clearly the findings described in the text. Undoubtedly the original films showed the changes clearly. These are minor faults, and this book can be warmly recommended to all who are interested in the subject of tuberculosis.

—*Richard H. Meade.*

THE MONOGRAPH entitled *A endoscopia abdômino-pelviana em ginecologia*[8] is the outgrowth of the author's teaching experience in conducting a course of clinical gynecology at the University of São Paulo.

It is stated that laparoscopy as a diagnostic procedure is not an invention of the present age. Man's curiosity to peer into intra-abdominal problems by means of some form of viewing instrument dates back to 1878, when a type of cystoscope was invented by Max Nitze and used on cadavers. Since then a considerable number of investigators and instruments have been forthcoming and laparoscopy has assumed a position of diagnostic importance, particularly in foreign countries despite its lag in the United States.

Gorga's monograph will definitely aid in removing many of the misconceptions concerning laparoscopy. Although the indications for laparoscopy are numerous the preponderance appears to be for gynecologic conditions. It is contended that laparatomies for diagnostic purposes alone should be strictly condemned and laparoscopy employed.

Numerous contraindications are recorded. In general it may be stated that when there is an acute process laparoscopy should be foregone.

Various types of instruments are enumerated and the technique of employing them in various anatomic areas is shown. The remaining half of the monograph is devoted to case reports and experiences with the laparoscope under various conditions and circumstances.

From this experience it is concluded that laparoscopy is harmless and the complications are for the most part not serious. Its usefulness as a biopsy instrument is second only to laparotomy which, it is maintained, should not be performed until the patient has had the benefit of laparoscopy.—*Stephen A. Zieman.*

[8]A ENDOSCOPIA ABDÔMINO-PELVIANA EM GINECOLOGIA. By Paulo Gorga. 280 pages, 84 illustrations. São Paulo, 1954.

THE VOLUME entitled *The Biliary Tract*[9] includes discussions on the liver, gallbladder, bile duct, and pancreas, although comparatively little space is devoted to the liver. Individual chapters are devoted to anatomy, physiology, and pathology. Much of the data represents the author's own research work. It is doubtful that many surgeons operating on the common duct and sphincter of Oddi would agree with the author's experience and statement (p. 32) that, "In only 3 per cent does the common channel occupy more than two-thirds of the papilla." In this reviewer's experience the figure appears to be much higher.

Occasionally, the author's attempt to cover a lot of ground leaves misleading impressions, as for example on page 138 where he closes the paragraph on islet cell adenoma of the pancreas with the statement that "recovery follows the administration of sugar by mouth or vein." Another statement concerning the surgical therapy is needed. However, these details are more than compensated by the authoritative and accurate way in which the material is presented. The young surgeon will find the numerous tables of "normals" on pages 198 to 203 very useful. The techniques of cholangiography and other important tests are described in sufficient detail to be of much value to most readers. A concise description of the technique of the more common operations on the biliary tract is given. The bibliography is extensive and up-to-date. The book will be found interesting and instructive to all readers interested in this field. —*Warren H. Cole.*

IN THE THIRD EDITION of the volume entitled *Lehrbuch der Geburtshilfe*,[10] the senior author again has the assistance of Bickenbach and of his artist, Droysen. The authors point out that during the last few years there have been many changes in our knowledge of obstetrics, not so much in classical obstetrics as in the branches of medicine which are allied with obstetrics, especially physiology, pharmacology, endocrinology, serology, internal medicine, and pediatrics. Since 90 per cent of all labors are normal, the chief function of the obstetrician should be prophylactic or preventive, that is he should see to it that labor remains physiologic, and he should protect the patient against complications. Especially should he be careful that he himself does not produce trouble, particularly by the use of oxytocics and unnecessary obstetric operations.

The chapters which were especially rewritten are those dealing with complications of pregnancy such as diabetes, blood diseases, and tuberculosis, and the chapter on the conduct of the third stage of labor.

There are a few minor criticisms. Disturbances of blood clotting such as afibrinogenemia are mentioned in only one sentence in the section on abruptio placentae; there is still a description with illustrations of internal measurements of the true conjugate diameter with the Bylicki-Gauss pelvimeter and the description with illustrations of aorta compressors is retained.

[9]THE BILIARY TRACT; WITH SPECIAL REFERENCE TO THE COMMON BILE DUCT. By Julian A. Sterling, A.B., M.D., M.Med. Sc., Sc.D., F.A.C.S. 424 pages, 94 illustrations. $10.00. Baltimore: The Williams & Wilkins Co., 1955.

[10]LEHRBUCH DER GEBURTSHILFE. By Prof. Dr. Heinrich Martius. With the assistance of Prof. Dr. Werner Bickenbach and Käthe Droysen. 3rd rev. ed. 757 pages, 777 illustrations. $14.25. Stuttgart: Georg Thieme Verlag, 1956.

As was said about the second edition, there is ample evidence in this book that the authors have had very extensive experience, are excellent teachers, and are conservative in their recommendations of the conduct of pregnancy and labor. The illustrations (a few less than in the previous edition) are of the highest quality and definitely instructive. Again the authors and the publishers are to be congratulated on this outstanding book. —*J. P. Greenhill.*

THE PURPOSE OF THE VOLUME entitled *I tumori primitivi dello spazio retroperitoneale*[11] by Vittorio Pettinari is to offer a complete description and classification of the tumors of the retroperitoneal region. This is not a simple task since it is necessary to reduce to a topographic criterion numerous tumors of diverse origin and even more varied structure. In the beginning of this essay the author presents a very detailed definition of the anatomic limits of the retroperitoneal space, with minute descriptions of the organs and of the embryonic residues contained therein.

In regard to the anatomicopathologic part, the author reports interesting statistics related to percentage of occurrence in relation to the different anatomic sections of the retroperitoneal space; the distribution of the tumors with respect to sex and the age; and the percentage of occurrence of metastases. All these statistics have been compiled from 1,032 case studies described by several authors from 1950 to 1955.

Interesting, and with excellent photographic documentation from the author's personal cases, is the study of the histogenetic aspect of the tumors, usually not easy to interpret because of the difficulty in discovering and studying the initial stages. The tumors are classified as follows: (1) mesenchymomas, formed by mixed varieties of tissues of mesenchymal origin—(number 57, 8 per cent). (2) tumors growing from embryonic residues (solid or cystic teratomas; tumors with suprarenal structures; chorionepitheliomas; mesotheliomas). (3) tumors originating from the nervous system (from the nervous trunks or, more frequently, from the sympathetic system), frequency, 11 per cent.

In regard to the clinical characteristics, he defines some important principles of diagnosis: semeiologic and radiologic character of the retroperitoneal position; prolonged latency, with slow growth and late appearance of major trouble; wide possibility of development in any direction, with limited mobility and without well defined limits; and lack of a direct symptomatology involving specific organs (only present at a late stage).

From a statistical observation of the cases described in the literature, he notes that a general symptomatology (loss of weight, anemia, asthenia) was present in 22 per cent of cases; local findings (palpable mass, pain) were present in 22 per cent of cases; in 23 per cent there were symptoms pertaining to the gastrointestinal system (such as dyspeptic symptoms, meteorism, sometimes obstruction, and hemorrhage); in 7 per cent of cases symptoms were related to the urinary system and were exclusively mechanical (compression, displacement, angulation of the ureters), or were those of invasive action of the tumor. Less frequently there were gynecologic or thoracic symptoms, or trouble in the lower limbs.

As a result of his own observations the author suggests the following methods of investigation: (1) *Indirect radiologic examination* of the neighboring organs to observe modification by displacement, compression, traction, especially of the diaphragm, stomach, duodenum, ileum, colon (displaced more by the tumors with lateral localization than by those with a median position), ureters, and kidneys. The following tests could also be useful: aortography—for the determination of displacement of the aorta, or for the visualization of the renal artery (p. 266) or for the study of the vascularization of the tumor; abdominal phlebography—good cavagraphs from his personal cases (pp. 237, 266); splenoportography (p. 237) and renal phlebography. (2) *Direct radiologic examination*, executed without means of contrast material, often with the help of the pneumoretroperitoneum, which is very useful especially if combined with stratigraphic examination (pp. 234, 235, 237, 266).

Another useful practice is observation with the infrared rays of the superficial venous pattern of the abdominal wall—sometimes this examination was positive while the ordinary examination of the patient was negative (p. 228).

The author states that the serious prognosis is due chiefly to the difficulty in making an early diagnosis; to the necessity of major operations because of the usual great volume and diffusion; and to the tendency toward a recurrence and to malignant change.

The author further states that surgery is the only effective treatment; it has to be performed whenever the tumor is discovered. It is possible to follow several routes of access (transperitoneal, abdominothoracic, retroperitoneal), according to the localization, extension, and invasion present in each particular case.

This monograph which ends with a detailed exposition of 15 cases, is well presented and of considerable scientific interest. —*Luciano Mazzolani.*

THE SECOND EDITION of *Chest X-Ray Diagnosis*[12] amply accomplishes its purpose in providing a large collection of radiographs showing both common and rare conditions in which roentgen examination is of value.

This text and practical reference work combines over 30 years of experience, including recent advances, with an effective, clear text. The radiographic reproductions are accompanied by brief, informative legends correlating with the text, and the bibliographic references at the end of most sections have been held to a minimum.

A usable index leads the reader directly to the problem; then the text illustrates and follows through with differential diagnosis.

A few of the new and revised topics are: hemorrhagic fever, broncholithiasis, intrathoracic hibernoma,

[11] I TUMORI PRIMITIVI DELLO SPAZIO RETROPERITONEALE. By Vittorio Pettinari. Relazione tenuta al LVII Congresso della Società Italiana di Chirurgia, Roma, 3-6 ottobre 1955. 283 pages, 29 illustrations. Roma: Edizioni Mediche e Scientifiche, 1955.

[12] CHEST X-RAY DIAGNOSIS. By Max Ritvo, M.D. 2nd ed., thoroughly rev. 640 pages, 633 illustrations on 426 figures and 1 color plate. $16.00. Philadelphia: Lea & Febiger, 1956.

atelectasis, hyaline disease of lung, tuberous sclerosis, cystic disease, parathyroid tumors, amyloidosis, primary tumors of the diaphragm, infrapulmonary pleural effusion, lung torsion after trauma, pericardial diverticulum, infectious mononucleosis, pulmonary hemosiderosis, accessory liver lobe, and the previously tested presentation of the more common chest diseases.

The section on congenital diseases of the heart and great vessels has been expanded and here, as well as throughout the remainder of the 640 pages, all significant advances are included.

Once again, this book is recommended for the student, the practitioner, the specialist, and the teacher. —*William E. Bundesen.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

THE NEUROSES IN CLINICAL PRACTICE. By Henry P. Laughlin, M.D. 802 pages. $12.50. Philadelphia and London: W. B. Saunders Co., 1956.

1956 MEDICAL PROGRESS; A REVIEW OF MEDICAL ADVANCES DURING 1955. Edited by Morris Fishbein, M.D. 389 pages. $5.50. New York, Toronto, London: The Blakiston Division, McGraw-Hill Book Co., Inc., 1956.

ELECTROCARDIOGRAPHY; FUNDAMENTALS AND CLINICAL APPLICATION. By Louis Wolff, M.D. 2nd ed. 342 pages, 199 illustrations. $7.00. Philadelphia and London: W. B. Saunders Co., 1956.

LA CHIRURGIE PELVIENNE APRÈS CLOISONNEMENT ABDOMINO-PELVIEN; CANCER UTÉRIN, RECTAL, VÉSICAL. By Henri Bompart and R. Michel-Béchet. 82 pages, 15 illustrations. 750 fr. Paris: Masson & Co., 1956.

TUBERCULOSE UTÉRO-ANNEXIELLE; ASPECTS ACTUELS-DIAGNOSTIC TRAITEMENT. By Jules Bret and Robert Legros. 248 pages, 60 illustrations. 1.600 fr. Paris: Masson & Co., 1956.

CLINICAL RECOGNITION AND MANAGEMENT OF DISTURBANCES OF BODY FLUIDS. By John H. Bland, M.D. 2nd ed. 522 pages, 109 illustrations. $11.50. Philadelphia and London: W. B. Saunders Co., 1956.

A VENTURE FORWARD; A HISTORY OF THE AMERICAN COLLEGE OF HOSPITAL ADMINISTRATORS. Compiled under the direction of the History Committee by Ira A. Kipnis. 145 pages, illustrated. $5.00. Chicago: American College of Hospital Administrators, 1955.

THE TRUTH ABOUT CANCER. By Charles S. Cameron, M.D. 268 pages. $4.95. Englewood Cliffs, New Jersey: Prentice-Hall, Inc., 1956.

ORTHOPEDICS AND OPERATIVE TRAUMATOLOGY. By B. Boytchev, B. Conforty, and K. Tchokanov. 657 pages, 590 illustrations. (Printed in Bulgarian.) Sofia: Drzhavno "Science and Arts" Publishers, 1955.

TRANSACTIONS OF THE SEVENTY-FOURTH MEETING OF THE AMERICAN SURGICAL ASSOCIATION. Held at the Hotel Cleveland, Cleveland, Ohio, April 28, 29, 30, 1954. Vol. 72. Edited by Brian Blades, M.D. 417 pages, illustrated. Philadelphia: J. B. Lippincott Co., 1955.

STUDIES ON FERTILITY. Edited by R. G. Harrison, M.A., D.M. Vol. VII of the Proceedings of the Conference of the Society for the Study of Fertility. 156 pages, illustrated. $5.00. Springfield, Ill.: Charles C Thomas; Oxford: Blackwell Scientific Publications, 1955.

TUMORS OF THE SKIN. By Herbert Conway, B.S., M.S., M.B., M.D., F.A.C.S. 267 pages, 178 illustrations. $13.50. Springfield, Ill.: Charles C Thomas, 1956.

THE DIAGNOSIS AND TREATMENT OF POSTURAL DEFECTS. By Winthrop Morgan Phelps, M.D., Robert J. H. Kiphuth, M.P.E., and Charles Weer Goff, M.D. 2nd ed. 190 pages, 87 illustrations. $6.50. Springfield, Ill. Charles C Thomas, 1956.

RECHERCHES SUR LA CONSTITUTION DE L'OS ADULTE. By J. Vincent. Dissertation présentée devant la faculté de médecine épreuve de l'agrégation de l'enseignement supérieur. 153 pages, 41 illustrations. Bruxelles: Éditions Arscia, 1955.

RADIUM THERAPY; ITS PHYSICAL ASPECTS AND EXTENSIONS WITH RADIOACTIVE ISOTOPES. By C. W. Wilson, M.Sc., Ph.D., F.Inst.P. Foreword by Sir Stanford Cade, F.R.C.S. 2nd ed. 286 pages, 73 illustrations. $7.50. Baltimore, Md.: The Williams & Wilkins Co.; London: Baillière, Tindall & Cox, 1956.

A HANDBOOK OF MEDICAL HYPNOSIS; AN INTRODUCTION FOR PRACTITIONERS AND STUDENTS. By Gordon Ambrose, L.M.S.S.A., and George Newbold, M.B., B.S., M.R.C.S., M.M.S.A., D.R.C.O.G., D.C.H. Forewords by William Moodie, M.D., F.R.C.S., and William S. Kroger, M.D. 255 pages. $5.00. Baltimore, Md.: The Williams & Wilkins Co.; London: Baillière, Tindall & Cox, 1956.

MIDWIFERY; PRINCIPLES AND PRACTICE FOR PUPIL MIDWIVES, TEACHER MIDWIVES AND OBSTETRIC DRESSERS. By R. Christie Brown, M.B., M.S., F.R.C.S., Barton Gilbert, B.Sc., M.D., F.R.C.S., Donald B. Fraser, M.A., B.M., B.Ch., F.R.C.S., and Richard H. Dobbs, M.D., F.R.C.P. 4th ed. 892 pages, 223 illustrations. $5.00. Baltimore, Md.: The Williams & Wilkins Co.; London: Edward Arnold (Publishers) Ltd., 1956.

THE FLAVONOIDS IN BIOLOGY AND MEDICINE; A CRITICAL REVIEW. By Maurice E. Shils, Sc.D., and Robert S. Goodhart, M.D. 101 pages, 8 illustrations. $2.00. New York: The National Vitamin Foundation, Inc., 1956.

THE ROCHESTER REGIONAL HOSPITAL COUNCIL. By Leonard S. Rosenfeld, M.D., M.P.H., and Henry B. Makover, M.D. 204 pages. $3.50. Published for the Commonwealth Fund. Cambridge, Mass.: Harvard University Press, 1956.

IN THE DOCTOR'S OFFICE; THE ART OF THE MEDICAL ASSISTANT. By Esther Jane Parsons. Illustrations by Jean McConnell. 2nd ed. 326 pages, illustrated. $3.95. Philadelphia and Montreal: J. B. Lippincott Co., 1956.

ANALGESIA FOR MIDWIVES. By Hilda Roberts, M.R.C.S. 68 pages, 25 illustrations and 5 color plates. $3.50. Baltimore, Md.: The Williams & Wilkins Co.; Edinburgh and London: E. & S. Livingstone Ltd., 1955.

CARDIOVASCULAR INNERVATION. By G. A. G. Mitchell, O.B.E., T.D., M.B., Ch.M., D.Sc. Foreword by Sir Geoffrey Jefferson. 356 pages, 217 illustrations. $11.00. Baltimore, Md.: The Williams & Wilkins Co.; Edinburgh and London: E. & S. Livingstone Ltd., 1956.

GYNECOLOGIC CANCER. By James A. Corscaden, Ph.B., M.D. 2nd ed. 546 pages, 116 illustrations. $10.00. Baltimore, Md.: The Williams & Wilkins Co., 1956.

CAMPBELL'S OPERATIVE ORTHOPAEDICS. Edited by J. S. Speed, M.D., and Robert A. Knight, M.D. 3rd ed., Vols. I and II. 2260 pages, 1323 illustrations. $40.00. St. Louis: The C. V. Mosby Co., 1956.

AMERICAN COLLEGE OF SURGEONS

WARREN H. COLE, Chicago, *President*

DANIEL C. ELKIN, Lancaster, Kentucky, *President-Elect*

PRELIMINARY PLANS FOR THE 42nd CLINICAL CONGRESS THE CIVIC AUDITORIUM, SAN FRANCISCO, CALIFORNIA OCTOBER 8 TO 12, 1956

THE DISTINGUISHED scientist and engineer, Vannevar Bush, will give the Martin Memorial Lecture on the opening evening of the Congress, at 8:30. At the Convocation, on Friday evening, Dr. Daniel C. Elkin will give the Presidential Address. On Wednesday evening the Motion Picture Symposium, featuring the unusual in surgery, will be held.

Doctor Bush is world renowned also as an inventor and executive. From 1939 to January 1956, he served as President of the Carnegie Institution of Washington. In 1940, he was appointed Chairman of the National Defense Research Committee, and the following year he became Director of the newly established Office of Scientific Research and Development. In these two offices, he was a central figure in the development of nuclear fission. As a member of the top policy group headed by the President and as Chairman of the Military Policy Committee, Doctor Bush shared responsibility for the determination of policy throughout the program. In response to a request from the President, in July 1945, Doctor Bush prepared a report under the title "Science, the Endless Frontier" which included studies by eminent scientists, engineers, and educators, making specific proposals for the best use of the scientific skill of the nation for the general good.

Doctor Bush is internationally known too for independent research and inventions in many areas, from a new type of photographic composing machine to three machines facilitating biologic research: an automatic microtome for cutting and mounting thin sections of embedded biologic specimens, an electric micromanipulator for precise microbiologic and microphysical investigations, and a band saw microtome for cutting thin sections of gross anatomic specimens. He has also developed a new method of cutting and mounting sections of frozen tissue. He is the recipient of distinguished awards from the National Academy of Sciences, the Scientific Research Society of America, the American Society of Engineering Education, and many other scientific organizations.

General Sessions

General sessions will begin promptly at 10 a.m. Monday with a panel discussion on "Surgery of the Adrenal Glands," with Oliver Cope serving as the moderator. Collaborators include Peter H. Forsham, James T. Priestley, and Harold A. Zintel. "Prophylaxis in Dissemination and Implantation of Cancer" will follow with Warren H. Cole as the moderator. Dr. Cole's collaborators are Lauren V. Ackerman, Rupert Turnbull, John M. Waugh, and Frank C. Wheelock, Jr. A panel on "Hyperthyroidism" will be next, with Brown M. Dobys serving as the moderator, collaborators to be announced.

"Pelvic Pain in Women" is the topic for the Tuesday afternoon session at 1:30. Langdon Parsons is the moderator, and the collaborators

are Otto Aufranc, Laman A. Gray, Karl H. Martzloff, and Henry M. Weyrauch.

The Symposium on Trauma will begin at 2 p.m., with R. Arnold Griswold presiding. Topics and speakers will be:

Craniocerebral Injuries. EVERETT G. GRANTHAM.
Injuries to the Face and Neck. PAUL W. GREELEY.
Injuries to the Thorax. PAUL C. SAMSON.
Injuries to the Abdomen. HOWARD E. SNYDER.
Injuries to the Soft Tissues of the Extremities. OSCAR P. HAMPTON, JR.
Injuries to the Skeletal System. JAMES K. STACK.
Priorities in Treatment. JOSEPH R. SHAEFFER.

"Surgical Management of Duodenal Ulcer" will be discussed at 3:30 p.m., with Jonathan E. Rhoads as moderator, and, as collaborators, James D. Hardy, Henry N. Harkins, Richard Warren, and Donald R. Webster.

On Wednesday afternoon at 1:30 "Hiatal Hernia and Esophagitis" will be the topic with Stuart W. Harrington as the moderator. Collaborating will be Philip R. Allison of Cambridge, Robert C. Laird, Herbert W. Schmidt, and James D. Rives.

The Symposium on Cancer will begin at 2 p.m. on Wednesday. Danely P. Slaughter is the presiding officer. Topics and participants will be:

Explanation of the Cancer Program of the American College of Surgeons. DANELY P. SLAUGHTER.
Review of Current Status of Chemotherapy. JOSEPH H. BURCHENAL.
The Principles and Techniques of Soft-Part Resection for Sarcomas. LEMUEL BOWDEN.
A Biometric Evaluation of Mammary Cancer. JOSEPH BERKSON.
The Diagnostic Significance of Lateral Tumors in the Neck. IAN MACDONALD.

Also on Wednesday afternoon, at 3:30, a panel on "What Antibiotics Should We Use, and When?" will be heard, with Champ Lyons as the moderator. Collaborators will include William A. Altemeier, Clayton H. Crosby, and Lowell A. Rantz.

"Burns" will be the panel topic on Thursday afternoon at 1:30, with John D. Martin, Jr. as the moderator. The collaborators will include Curtis P. Artz, Truman G. Blocker, Jr., and Boyd W. Haynes, Jr. The Symposium on Graduate Training in Surgery and the Surgical Specialties will follow with Frederick A. Coller as the chairman.

The historic Oration on Trauma, to be given this year by Michael L. Mason, will be heard at 3:15 in the afternoon. The subject is "The Treatment of Open Wounds."

"What's New in Surgery?"—a résumé of important research developments heard during the week's Forum on Fundamental Surgical Problems—will be heard Friday from 9 a.m. to 12 noon. Harris B. Shumacker, Jr. will preside.

Specialty Sessions

Topics, moderators and time of panel discussions are outlined briefly here. Collaborators will be announced in the next issue of this Journal:

OBSTETRICS AND GYNECOLOGY

MONDAY, 1:30–3 p.m.—Indications and Techniques in Induction of Labor. JAMES L. REYCRAFT, Moderator. 3:30–5 p.m.—Metabolic Implant of Surgery, Radiation, and Labor. MILTON L. MCCALL, Moderator.

TUESDAY, 1:30–3 p.m.—Pelvic Pain in Women. (This session also included under General Sessions.) LANGDON PARSONS, Moderator. 3:30–5 p.m.—Contrasted Methods in Treatment of Abruptio. CONRAD COLLINS, Moderator.

WEDNESDAY, 1:30–3 p.m.—Prematurity and Postmaturity. RUSSELL R. DE ALVAREZ, Moderator. 3:15–5 p.m.—Surgical Forum Session.

THURSDAY, 1:30–3 p.m.—Perineal Trauma. HAROLD L. GAINEY, Moderator.

FRIDAY, 3:15–4:45 p.m.—Surgical Standards in Treatment of Carcinoma of the Cervix. ERLE HENRIKSEN, Moderator.

NEUROLOGIC SURGERY

FRIDAY, 9-10:30 a.m.—Surgical Management of Intracranial Aneurysms and Arteriovenous Malformations. RUSSELL MEYERS, Moderator. 10:30–12 noon—Surgical Management of Cerebrovascular Disease. E. S. GURDJIAN, Moderator, and Chairman, Advisory Council for Neurological Surgery. 1:30–4:45 p.m.—Symposium. Topic to be announced in the next issue.

ORTHOPEDIC SURGERY

FRIDAY, 1:30–3 p.m.—Fractures of Tarsal and Metatarsal Bones. E. GEORGE CHUINARD. 3:15–4:45 p.m.—Differential Diagnosis and Treatment of Low Back Pain and Sciatica. CLARENCE H. HEYMAN.

PLASTIC SURGERY

FRIDAY, 1:30–3 p.m.—Reconstructive Surgery of the Neck. DONALD M. GLOVER, Moderator. 3:15–4:45 p.m.—Reconstructive Surgery of the Eyelids and Orbital Region. WILLIAM S. KISKADDEN, Moderator.

THORACIC SURGERY

FRIDAY, 1:30–3 p.m.—Selective Pulmonary Resection. ROBERT R. SHAW, Moderator. 3:15–4:45 p.m.—Recent Developments in Cardiac Surgery. ALFRED BLALOCK.

UROLOGY

MONDAY, 3:30–5 p.m.—Hypospadias. EDGAR BURNS, Moderator.

TUESDAY, 1:30–3 p.m.—Evaluation of Isotopes in the Treatment of Carcinoma of the Prostate and Bladder. VINCENT J. O'CONOR, Moderator.

WEDNESDAY, 1:30–3 p.m.—Surgical Injuries of the Lower Urinary Tract. WILLIAM NILES WISHARD, JR.

FRIDAY, 1:30–3 p.m.—Management of Obstructions of the Upper Urinary Tract. REED M. NESBIT, Moderator.

OTOLARYNGOLOGY

THURSDAY, 1:15–3:15 p.m.—Symposium on Mobilization of the Stapes in Otosclerosis. HOWARD HOUSE, Moderator. Participants will be announced in the next issue.

OPHTHALMOLOGY

WEDNESDAY, 2–5 p.m.—Symposium. Topics and participants to be announced.

There will be one session each for Otolaryngology and Ophthalmology instead of the usual three-day sessions because of the annual meetings of the American Boards of Ophthalmology and Otolaryngology and the Academy meeting of these two specialties to be held during and immediately following Congress week.

Postgraduate Courses

Classes will meet Monday through Thursday, with the exception of the course on Obstetrics and Gynecology, which will be held Monday through Friday. All courses are scheduled from 8:30 to 11:30 a.m. and the fee is $5.00 per course. Registration is permissible for one course only. Because seating will be limited and these classes are so popular, it is wise to register as soon as possible. As an added convenience course tickets will be mailed to you in advance. Courses and chairmen follow:

Preoperative and Postoperative Care. HENRY THOMAS RANDALL, New York.

Gastrointestinal Tract. WILLIAM P. LONGMIRE, JR., Los Angeles.

Diseases of the Liver, Biliary Tract, and Pancreas. J. ENGLEBERT DUNPHY, Boston.

Cardiovascular Surgery. F. A. SIMEONE, Cleveland.

Fractures and Dislocations. FLOYD H. JERGESON, San Francisco.

Obstetrics and Gynecology. PHILIP H. ARNOT, San Francisco.

Orthopedic Surgery. FREDERIC C. BOST, San Francisco.

Surgical Aspects of Pulmonary Disease. PAUL C. SAMSON, Oakland.

Forum on Fundamental Surgical Problems

Sixteen Forum sessions will be held this year. Sessions are scheduled for each morning and afternoon of Congress week. The program will again include one or more sessions for five special fields of surgery. Harris B. Shumacker, Jr. is Chairman.

Color Television

Under the direction of H. Glenn Bell and his assistant Maurice Galante, a stellar television program will be presented. J. Garrott Allen is the National Chairman. Two-way communication will be utilized again, as it was phenomenally successful last year. Operations will emanate from the H. C. Moffitt Hospital. Thirteen operations are scheduled for mornings and afternoons, Monday through Friday, with surgeons from Leland Stanford and University of California operating. Operations, operating surgeons, and times are indicated here, the co-ordinators and panels will be announced in the next issue:

MONDAY, 9-11:15 a.m.—Thyroidectomy for Tumor. H. H. SEARLS. 2-3:30 p.m.—Parathyroidectomy for Adenoma. LEON GOLDMAN. 3:30-5 p.m.—Radical Mastectomy for Carcinoma. H. GLENN BELL.

TUESDAY, 9-11:30 a.m.—Aortic Thromboendarterectomy. EDWIN J. WYLIE. 2–3:30 p.m.—Hiatus Hernia Repair. H. BRODIE STEPHENS. 3:30–5 p.m.—Common Duct Exploration. ORVILLE F. GRIMES.

WEDNESDAY, 9–11:30 a.m.—Combined Operation for Intraoral Malignancy. MAURICE GALANTE. 2–3:30 p.m.—Gastric Resection. HORACE J. MCCORKLE. 3:30–5 p.m.—Ventral Hernioplasty. VICTOR RICHARDS.

THURSDAY, 9–11:30 a.m.—Colectomy. ROBERT SCARBOROUGH. 2–3:30 p.m.—Intestinal Obstruction.

FRIDAY, 9–11:30 a.m.—Open Reduction of Ankle. LEROY C. ABBOTT. 2–3:30 p.m.—Surgical Correction of Hypospadias. DONALD R. SMITH.

A new feature to be added this year is a half-hour symposium, from 11:30 a.m. to 12 noon following the television program, featuring a panel of eminent surgeons from all over the

United States, who will discuss important current surgery. Visual materials of many types will be available, supplementing the topic discussed. The tentative program follows, participants to be announced in a future issue:

MONDAY—Surgical Aspects of Ammonia Intoxications.
TUESDAY—The Management of Metastatic Breast Cancer.
WEDNESDAY—Newer Methods of Urinary Diversion.
THURSDAY—Diagnosis and Treatment of Islet Cell Tumors.
FRIDAY—Portal Hypertension: Methods of Management.

Ciné Clinics

As in the past years, the Ciné Clinic program is to be a carefully planned, useful series. Surgeons who made the films will be present to answer questions from the audience. The following productions will be shown Tuesday through Friday:

Traumatic Diaphragmatic Hernia. WILLIAM E. ADAMS, Chicago.
Cesarean Hysterectomy. M. EDWARD DAVIS, Chicago.
Gastric Resection for Duodenal Ulcer. CLARENCE J. BERNE, Los Angeles.
Adrenalectomy. VICTOR RICHARDS, San Francisco.
Cholecystectomy and Operative Cholangiography. JOEL W. BAKER, Seattle.
Hernioplasty. HENRY N. HARKINS, Seattle.
Obstruction of Vena Cava with Replacement by Autograft. C. ROLLINS HANLON, St. Louis.
Heller Operation. LAURENCE S. FALLIS, Detroit.
Ventral Hernia. WALTER C. MACKENZIE, Edmonton.
Surgery of the Breast. PHILIP B. PRICE, Salt Lake City.
Surgery of the Breast. HERBERT H. DAVIS, Omaha.
Hernia in Infants. COLIN F. FERGUSON, Winnipeg.
Ulcerative Colitis. J. WILLIAM HINTON, New York.
Gastric Resection for Duodenal Ulcer. HOWARD A. PATTERSON, New York.
Peptic Ulcer. SAMUEL F. MARSHALL, Boston.
Unexplained Bleeding of Upper Gastrointestinal Tract. J. ENGLEBERT DUNPHY, Boston.
Surgery of Trauma, subject to be announced. ROBERT H. KENNEDY, New York.

Motion Pictures

A program of carefully selected films will be shown each morning and afternoon, Monday through Friday. The choice of films represents the considered thinking of an important committee which has worked diligently to create the best Congress program to date. Fellows and their film assignments follow:

Consultant on Ciné Clinics. GUSTAF LINDSKOG.
Plastic and Reconstructive Surgery. MICHAEL L. MASON.
Orthopedics. WILLIAM A. LARMON.
Obstetrics and Gynecology. JOHN W. HUFFMAN.
Urology. NORRIS J. HECKEL.
Thoracic and Children's Surgery. RUDOLF J. NOER.
Surgery of the Head and Neck. B. MARDEN BLACK.
Surgery of the Esophagus. GEORGE CRILE, JR.
Surgery of the Stomach and Intestine. CHARLES PUESTOW.
Biliary Tract Surgery. RICHARD B. CATTELL.

On Wednesday evening the Motion Picture Symposium will be held featuring the new and unusual in surgery. This program of short films, personally narrated by the author, has become one of the outstanding features of the Congress.

Advance Registration

Clinical Congress forms for advance registration, hotel accommodations, postgraduate courses, and transportation information have already been sent to Fellows of the College. Non-Fellows may obtain these forms by writing to the American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois. Early return of these forms is advisable to assure prompt receipt of your badge on your arrival, early choice of postgraduate courses, and satisfactory hotel accommodations.

Fees

No registration fee is charged Fellows if dues are paid to December 31, 1955. If dues are not paid, the fee is $20.00. No registration fee is charged members of the Candidate group. No fee is charged Surgical Residents provided a note of identification signed by their Chief of Surgery or Hospital Administrator accompanies the advance registration form. Non-Fellows pay a $20.00 fee, and members of the Federal Services pay $10.00. The Postgraduate Course fee is $5.00, payable by everyone taking a course.

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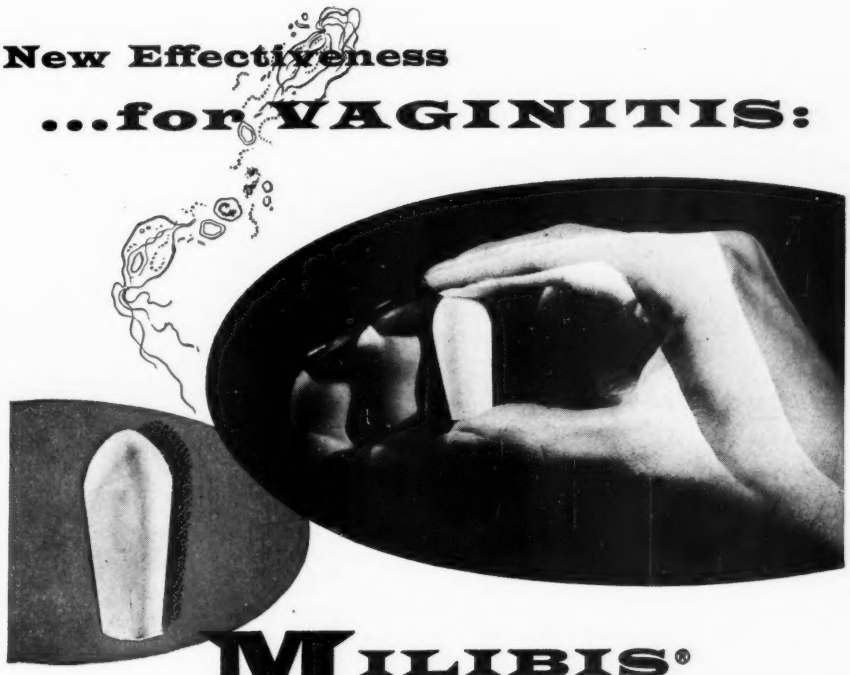

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